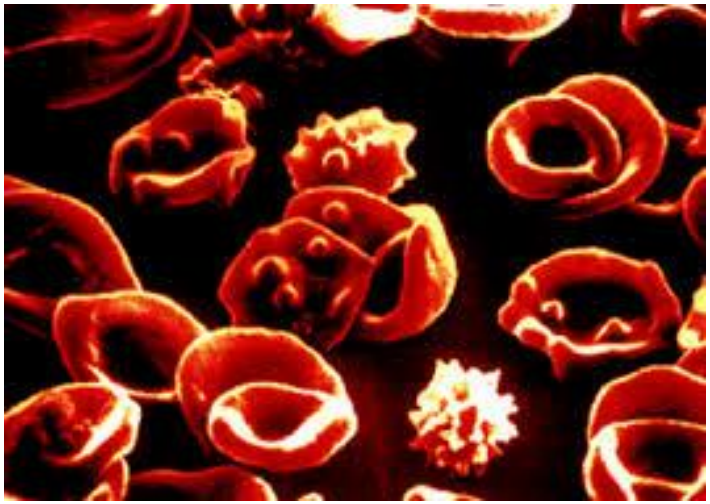
Management of Beta thalassemia/Hb E



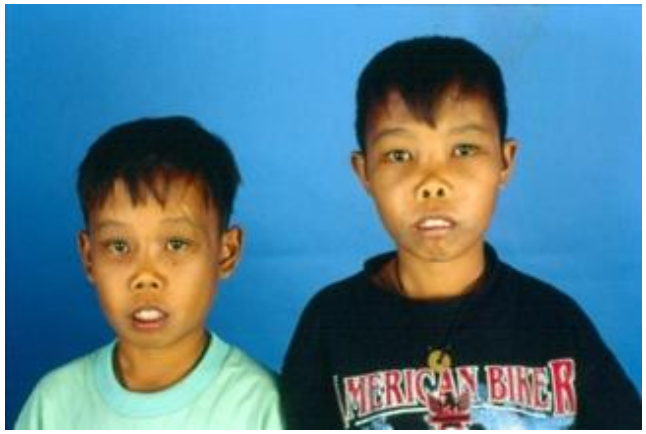
Akamon Tapprom MD.
Naresuan university hospital

Topics

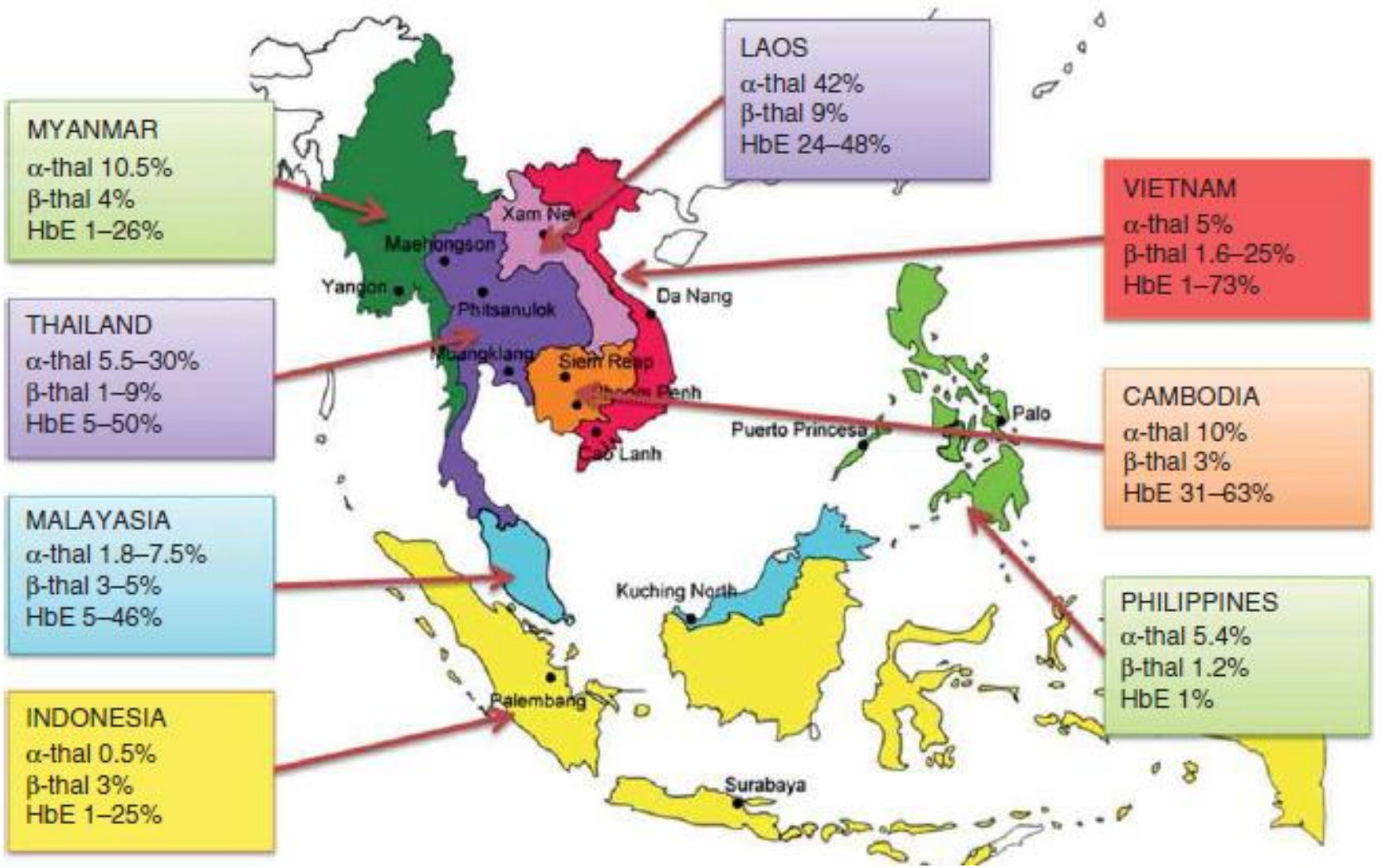
- Disease Background B thal/Hb E (TDT & NTDT)
- Optimal Transfusion in TDT
- Iron Overload and iron chelation
- Other treatment and other complication.

Beta thalassemia/Hb E

- one-half of all severe beta-thalassaemia worldwide.
- clinical variability mild and asymptomatic anaemia to a life-threatening disorder require transfusions from infancy.



Prevalence of thalassaemia and hemoglobinopathy in South East Asian countries



Viprakasit V et al. *Expert Opinion on Orphan Drug 2014*

Prevalence of Thalassemia/Hemoglobinopathies in Thailand (since 1980s')

NORTH

α-thalassemia	30%
α^0-thal.	5-12%
α^+-thal.	19-26%
β-thalassemia	9-10%
Hb E	8%

CENTRAL

α-thalassemia	20-25%
α^0-thal.	3.5%
α^+-thal.	16%
β-thalassemia	3%
Hb E	13-19%

NORTHEAST

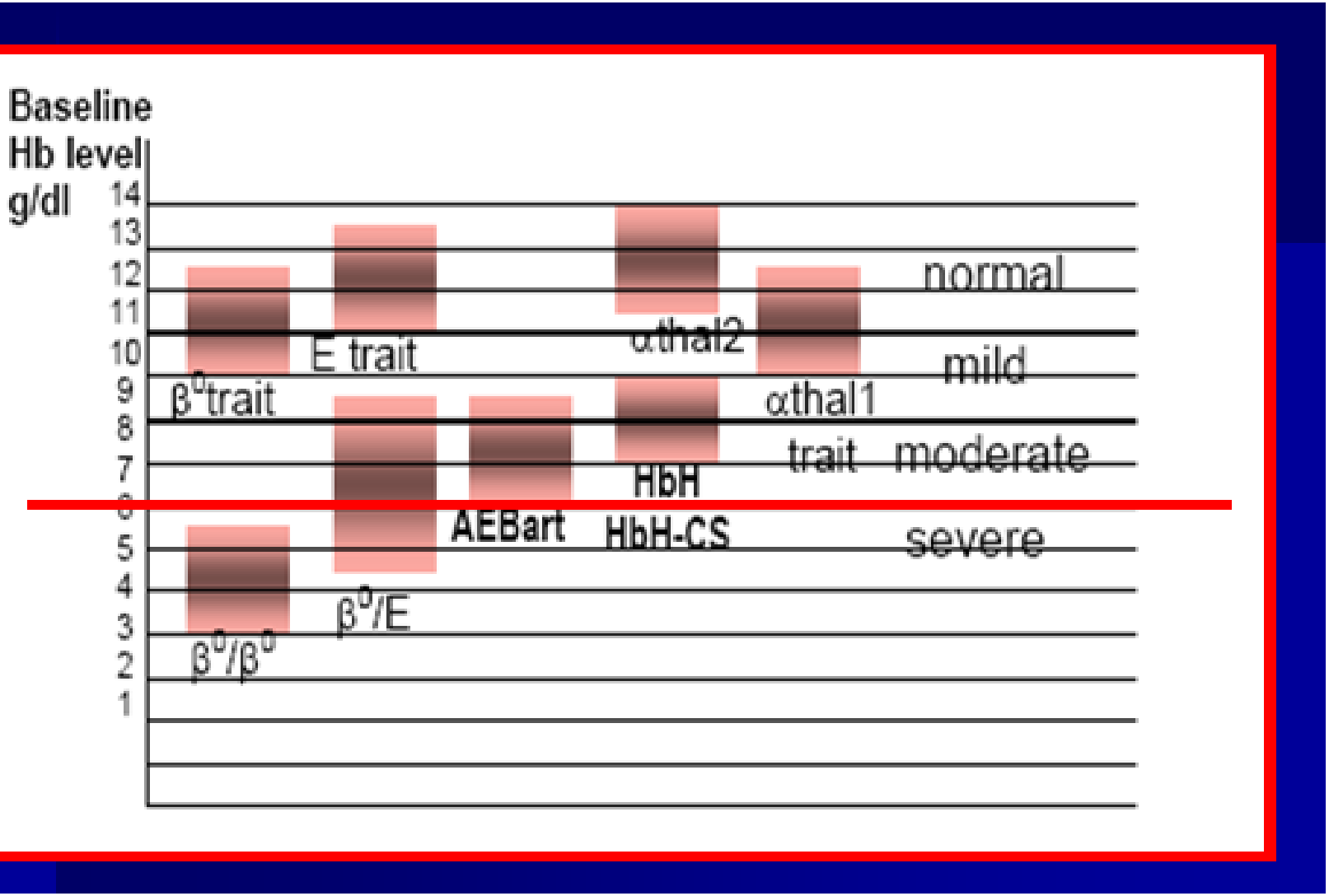
α-thalassemia	20%
α^0-thal.	3%
α^+-thal.	12%
β-thalassemia	6%
Hb E	20-60%

SOUTH

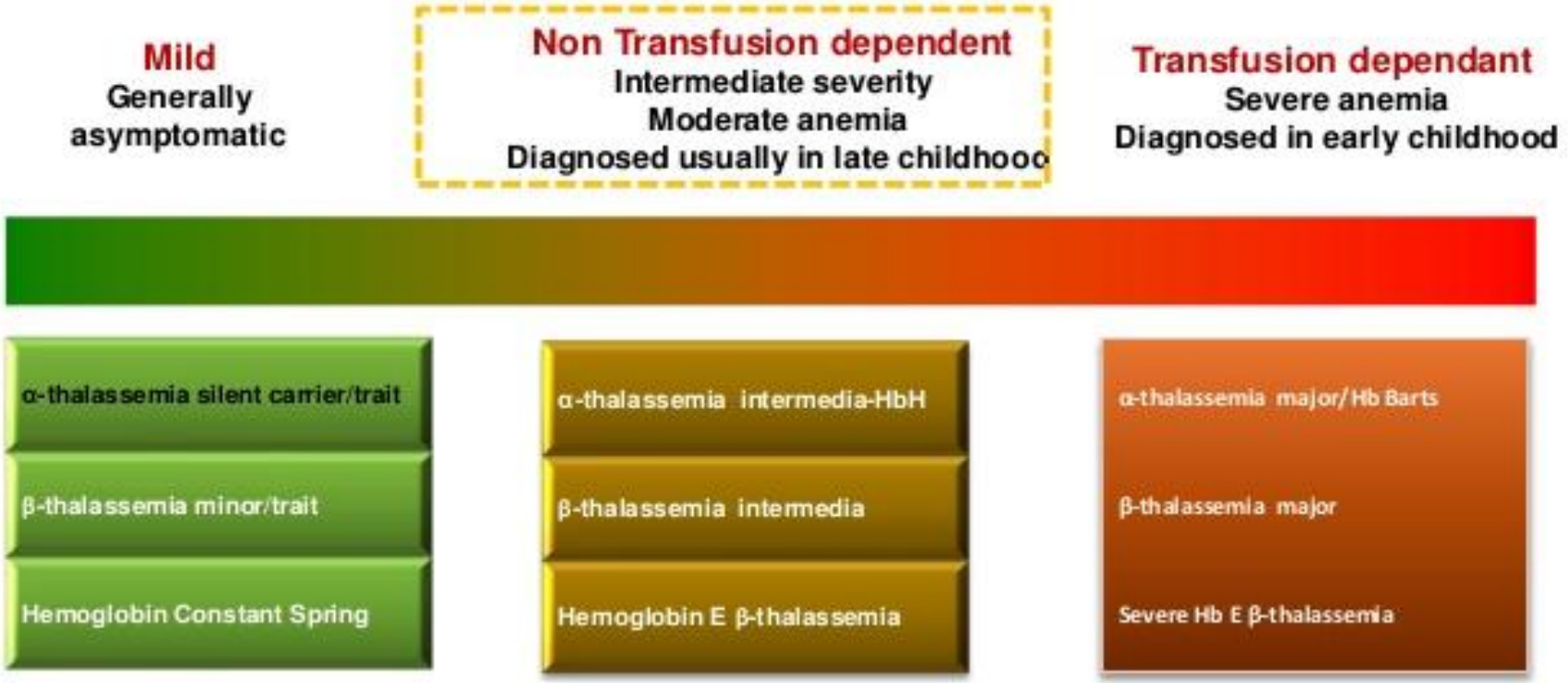
α-thalassemia	16%
α^0-thal.	2.5%
α^+-thal.	14%
β-thalassemia	2-4%
Hb E	9-11%

Courtesy of Thalassemia Foundation of Thailand

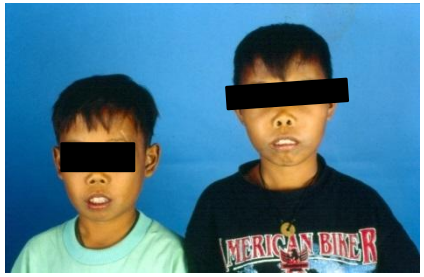
Severity of thalassemia



Thalassemia Clinical Severity Spectrum

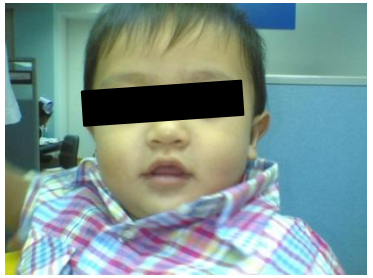


Clinical presentations: TDT vs NTDT



TDT

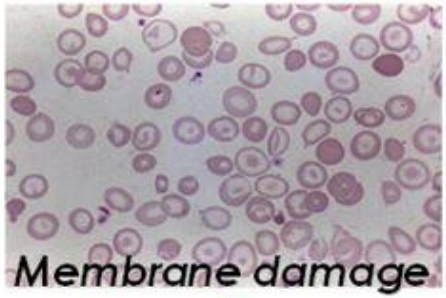
- Anemia / Jaundice
- Hepatosplenomegaly
- Hypersplenism
- Growth retardation
- Bony fracture
- Extramedullary haematopoiesis
- Iron overload
  - liver failure
  - endocrinopathies
  - cardiac failure
- Overt infection



NTDT

- Mild anemia / jaundice
- Require occasional tx
- Mild Hepatosplenomegaly
- Delay puberty
- Iron overload
  - liver complications
  - endocrinopathies

Pathophysiology of β–Thalassemia/Hb E Disease



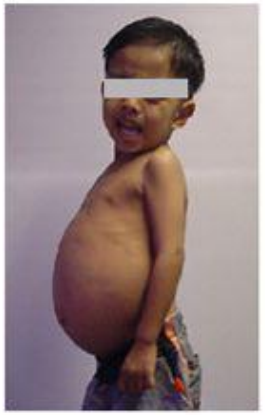
Membrane damage

β-Thalassemia genes

Excess unbound α-globin chains

Inclusion bodies
Increased RBC destruction

Iron excess



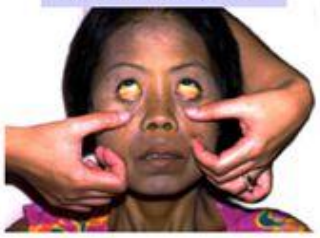
RE hyperplasia

Increased bilirubin production

Anemia

Gallstones

Jaundice



Massive erythropoiesis

Hepatosplenomegaly

Extramedullary hematopoiesis

Defective development

Bone changes

Iron overload

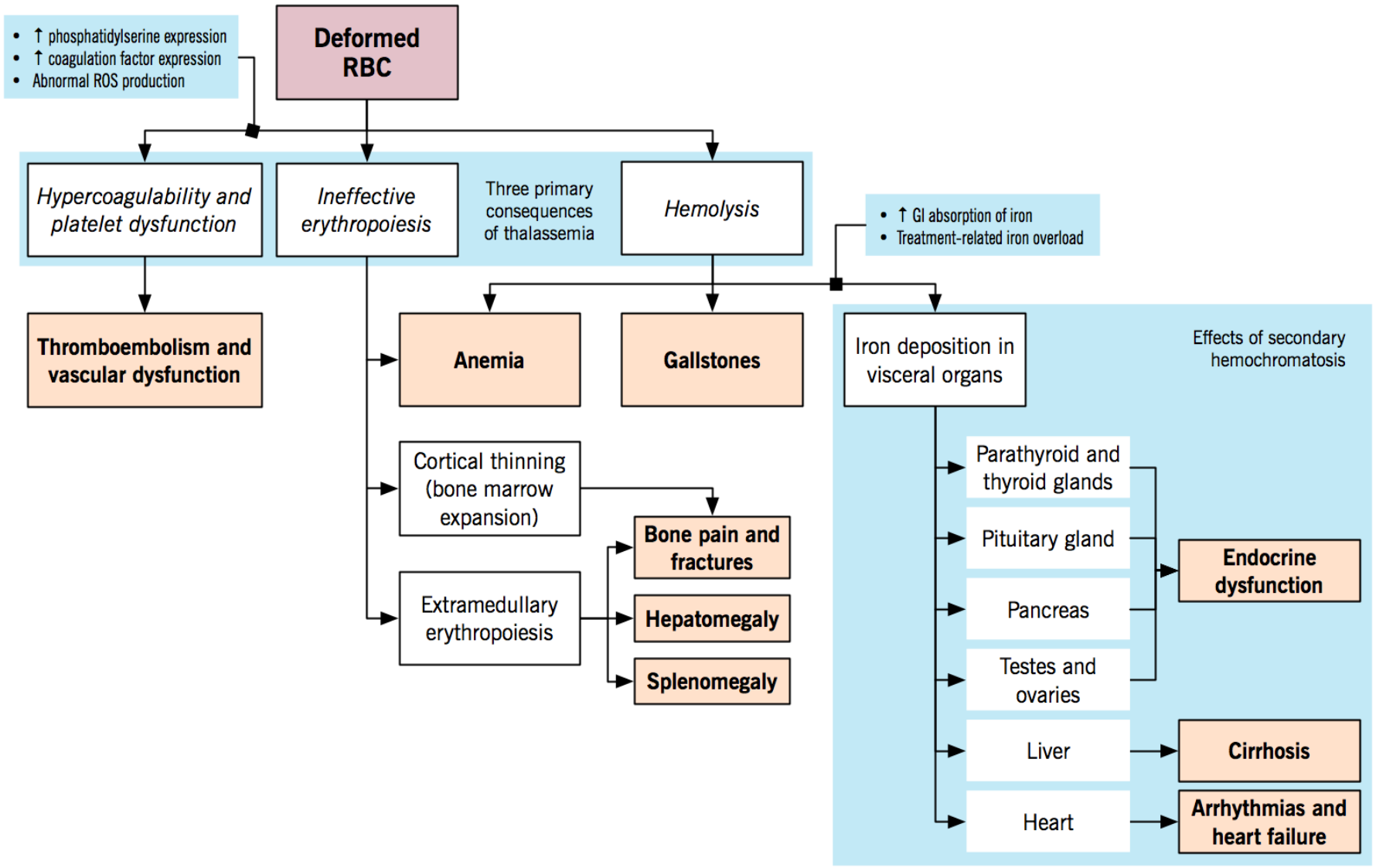
Blood transfusion

Cardiac failure, Cirrhosis, DM

Increased infection

Thalassemia | Mechanism of disease presentation and complications

Sultan Chaudhry



Prevalence of common complications in TI vs TM

Complication (% of patients affected)	TI		TM	
	Lebanon (n = 37)	Italy (n = 63)	Lebanon (n = 40)	Italy (n = 60)
Splenectomy	90	67	95	83
Cholecystectomy	85	68	15	7
Gallstones	55	63	10	23
Extramedullary hemopoiesis	20	24	0	0
Leg ulcers	20	33	0	0
Thrombotic events	28	22	0	0
Cardiopathy*	3	5	10	25
Pulmonary hypertension†	50	17	10	11
Abnormal liver enzymes	20	22	55	68
HCV infection	7	33	7	98
Hypogonadism	5	3	80	93
Diabetes mellitus	3	2	12.5	10
Hypothyroidism	3	2	15	11

*Fractional shortening < 35%. †Defined as pulmonary artery systolic pressure > 30 mmHg; a well-enveloped tricuspid regurgitant jet velocity could be detected in only 20 patients, so frequency was assessed in these patients only.

HCV = hepatitis C virus.

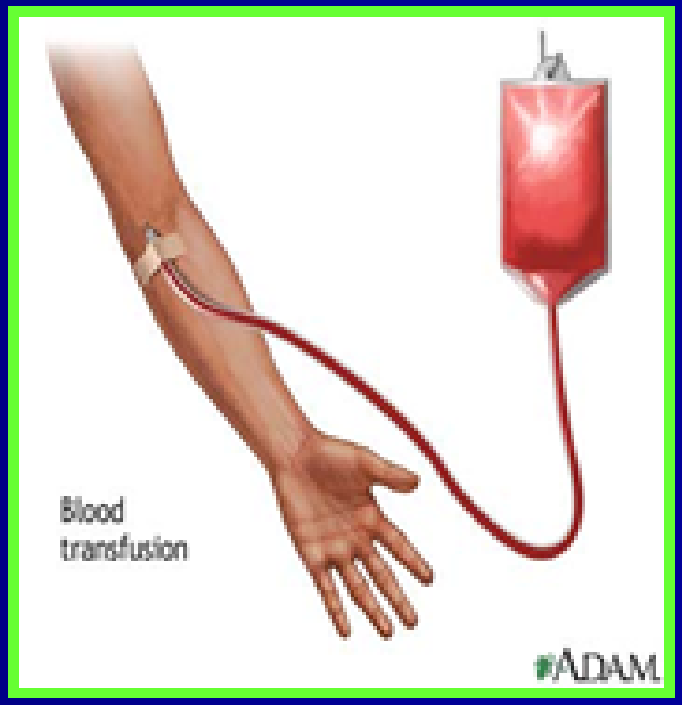
Taher A, et al. Blood Cells Mol Dis. 2006;37:12-20.

Treatment Beta thalassemia/Hb E

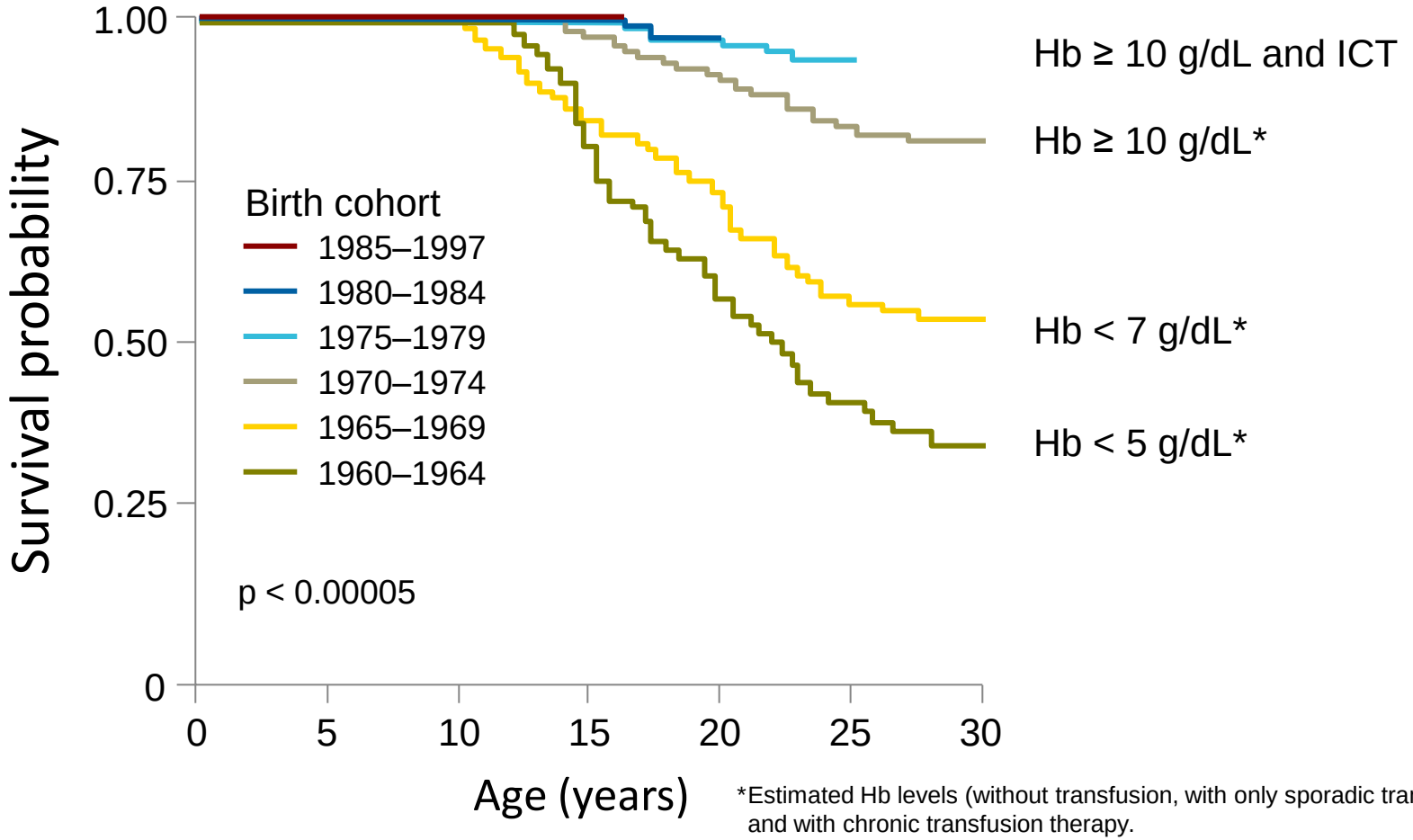
Optimal Transfusion in Transfusion-dependent Thalassemia (TDT)

PRC transfusion

- LPRC or LDRC (< 5 Days)
- 12-15 ml/kg (not more 2 U.)
- High transfusion :
  12-15 ml/kg q 2-3 wks.
  (Hb 9-12 g/dl)
- Low transfusion :
  10 ml/kg
  (Hb 8 g/dl)



Impact of transfusions on survival in TDT



*Estimated Hb levels (without transfusion, with only sporadic transfusions and with chronic transfusion therapy.

ICT, iron chelation therapy; TDT, transfusion-dependent thalassaemia.

Borgna-Pignatti C, et al. Haematologica. 2004;89:1187-93.

Transfusion programs in Transfusion-dependent Thalassemia (TDT)

Hypertransfusion (Hb > 9 g/dL) to relieve anemia and decrease ineffective erythropoiesis

- **Improved growth**
- **Less organomegaly**
- **Fewer fractures**
- **Less facial deformity**
- **Less impairment of normal activity**

Cazzola M, et al. Haematologica. 1997;37:135-40.
Wolman IJ. Ann NY Acad Sci. 1964;119:736-47.

Transfusion Regimen for TDT

- Red blood cells (RBC), Packed red cell (PRC)
- Leukocyte-poor red blood cells (LRBC)
  - Prevent febrile non-hemolytic transfusion reaction
- Leukocyte-depleted red blood cells (LDRBC)
  - Prevent febrile non-hemolytic transfusion reaction
  - Prevent HLA antibody formation
  - Decreased CMV transmission
- Two-unit red cells, single donor red cells (SDR)
  - Decreased donor exposure, risk of RBC antibody, risk of viral transmission
  - Prevent FNHTR, HLA antibody (leukocyte-depleted)

การให้เลือดในผู้ป่วยธาลัสซีเมีย ชนิดพึ่งพาเลือด หรือ Transfusion Dependent Thalassemia (TDT)

- รักษาค่า Hb ของผู้ป่วย**สูงกว่า 9 กรัม/ดล.** ตลอดเวลา และไม่ให้เกิน 14 กรัม/ดล
- โดยให้ เลือดกรอง หรือปั่นแยกเม็ดเลือดขาวออก ขนาด 12-15 มล./กก. หรือ 1-3 ยูนิตในผู้ใหญ่ **ทุก 2-6 สัปดาห์** ทำให้ผู้ป่วยมีคุณภาพชีวิตที่ดี การเจริญเติบโตปกติ โดยเฉพาะผู้ป่วยเด็ก

Current evidence for the benefit of transfusions in TI

- Failure to thrive in childhood in the presence of significant anemia
- Increasing anemia not attributable to rectifiable factors
- Delayed or poor pubertal growth spurt
- Progressive splenic enlargement
- Evidence of
  - bone deformities
  - clinically relevant tendency to thrombosis
  - leg ulcers
  - EMH
  - pulmonary hypertension
- Prior to surgical procedures

Guidelines for the clinical management of thalassaemia. 2nd rev ed. TIF 2008.

Iron overload in Thalassemia

Transfusion therapy results in iron overload

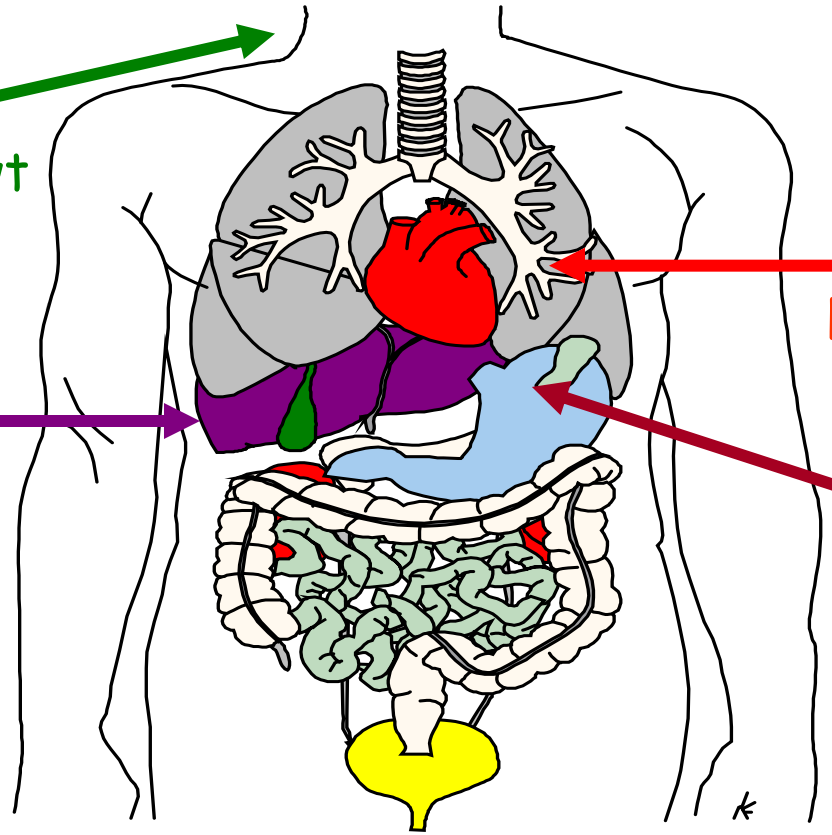
200–250 mg iron:
Whole blood: 0.47 mg iron/mL
‘Pure’ red cells: 1.16 mg iron/mL

- 1 blood unit contains 200 mg iron
- Overload can occur after 10–20 transfusions

Iron overload is an inevitable consequence of multiple blood transfusions

Porter JB. *Br J Haematol* 2001;115:239–252

Tissue Iron Concentrations in Transfusion-dependent Thalassemia Patients



Thyroid
Fe = 1.6 – 6.8% d wt

Liver
Fe = 3.7-6.8% d wt

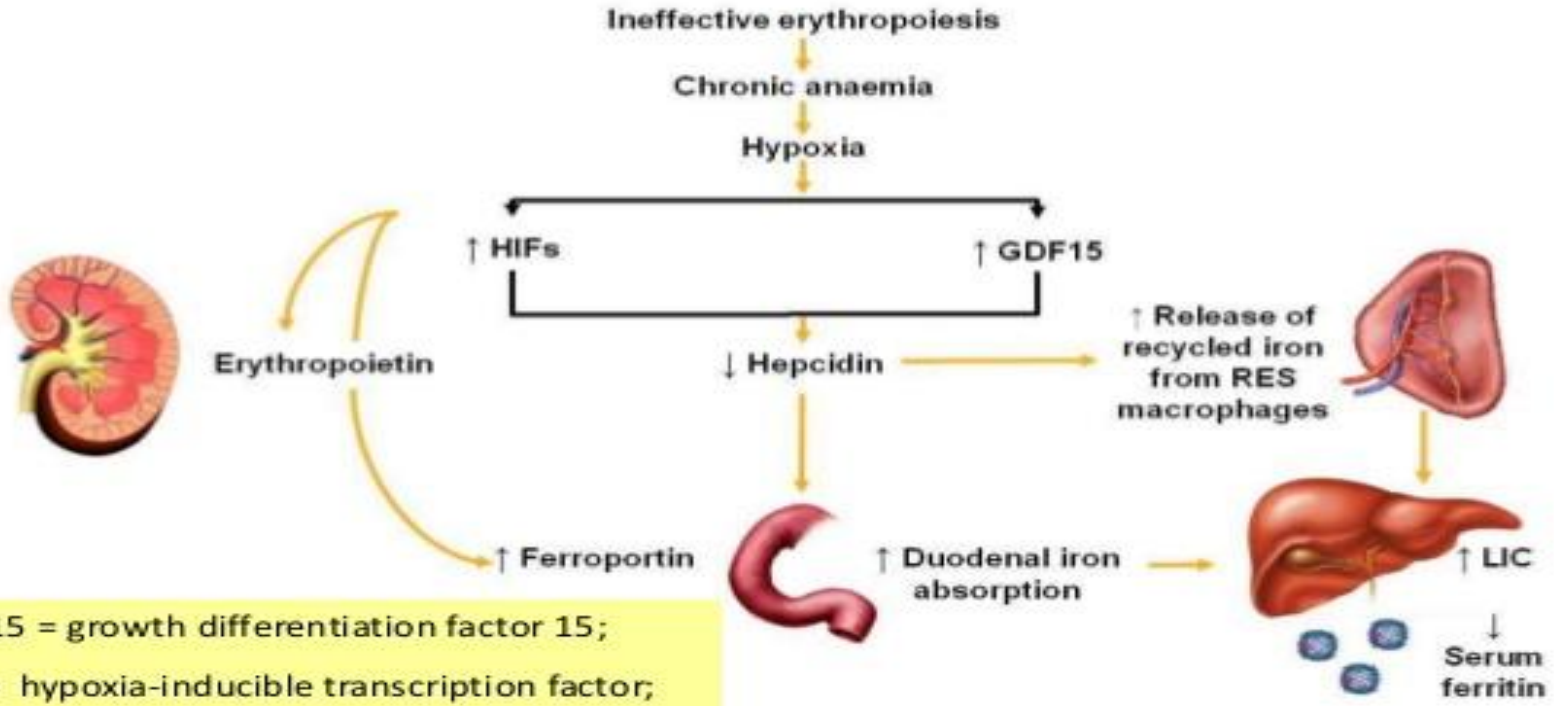
Heart
Fe = 0.6 –1.3% d wt

Pancreas
Fe = 1.4-3.9% d wt

Adapted from ***Modell & Berdoukas, 1984***

NTDT

Iron absorption in response to anemia



GDF15 = growth differentiation factor 15;

HIF = hypoxia-inducible transcription factor;

LIC = liver iron concentration;

RES = reticulo-endothelial system.

7

Complications of Iron Overload

Capacity of serum transferrin bind iron is exceeded

Non-transferring-bound iron NTBI in the plasma

Excess iron promotes the generation of free hydroxyl radicals, propagators of oxygen-related tissue damage

Insoluble iron complexes are deposited in body tissues and end-organ toxicity occurs

Cardiac failure

Liver cirrhosis/ fibrosis/cancer

Diabetes mellitus

Infertility

Growth Failure

Measurement of Iron overload

- **Serum ferritin**

  - useful low-cost measure

  - mornitor every 3-4 months

- **Liver iron concentration**

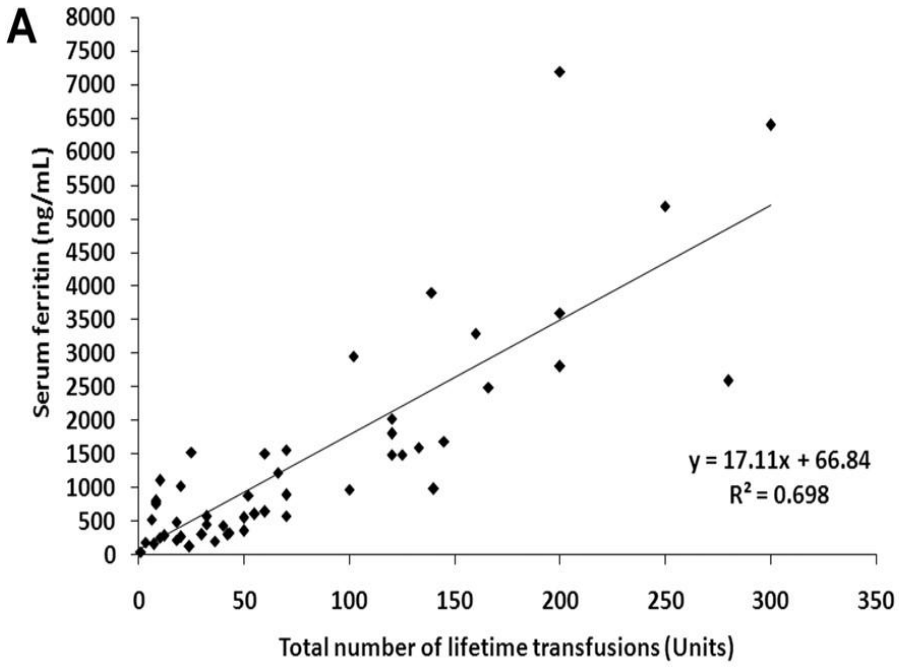
  - Best marker for total body iron

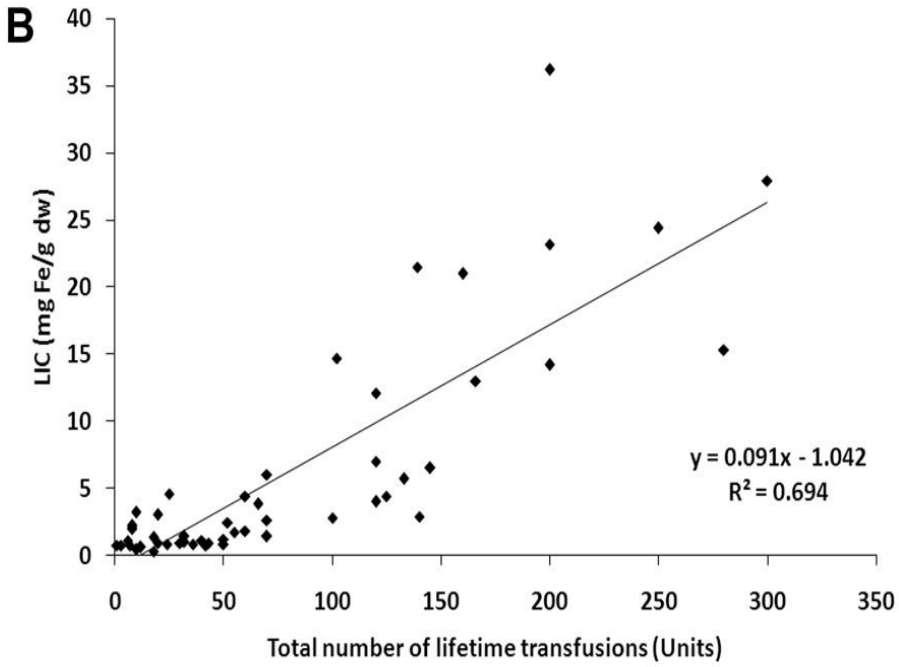
  - Value of **15** mg/g DW

(Cardiac dis., early death)

Thalassemia Major; transfusional hemosiderosis. The noxious effect of transfusions

Ferritin levels and liver iron content increase with number of transfusions

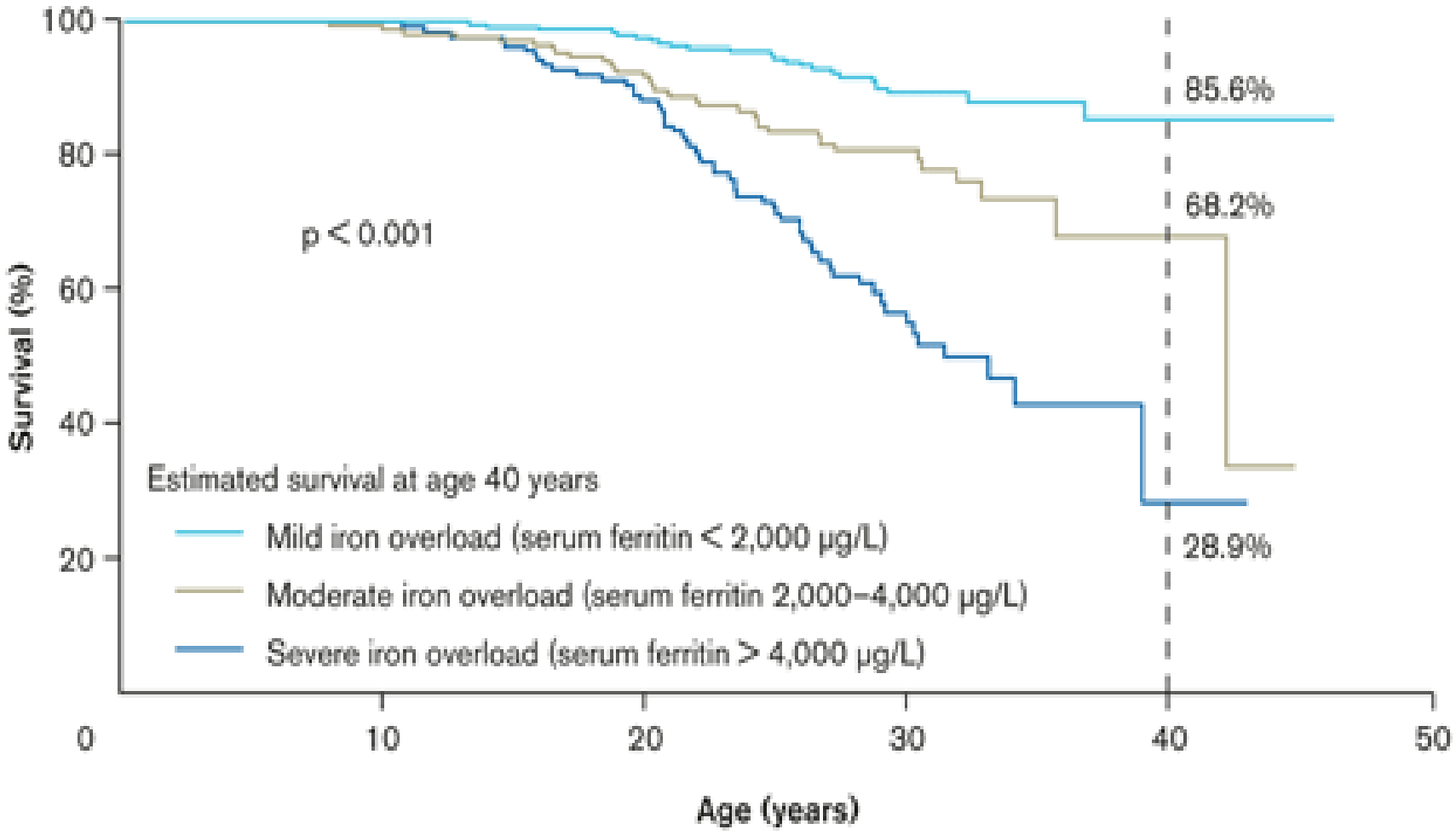




Total number of transfusions versus ferritin levels

Total number of transfusions versus liver iron content

Shortened survival in relation to iron overload; High ferritin levels predict early death



Ladis et al, 2005

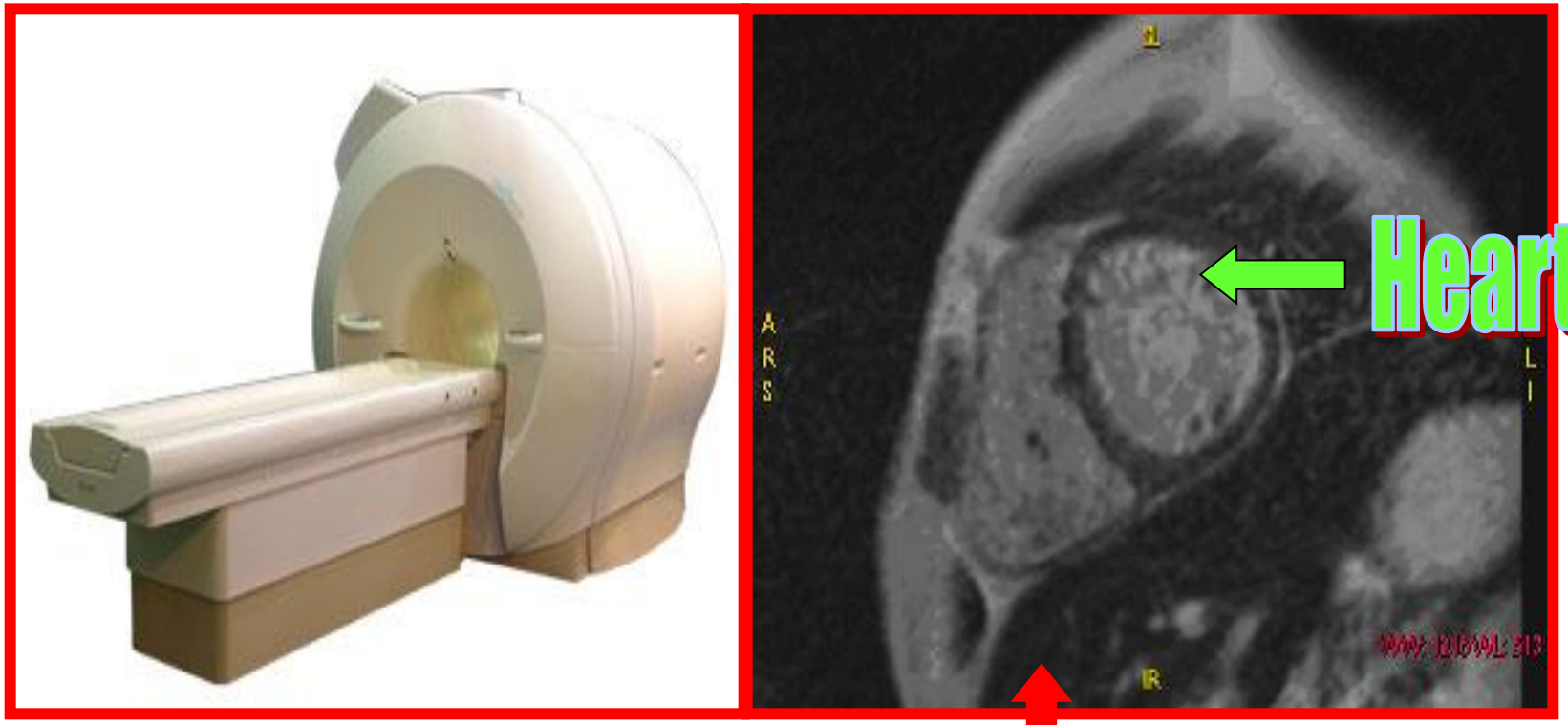
Measurement of Iron overload

- **Liver iron by MRI (R2-MRI)**
- **Cardiac iron by MRI(T2*-MRI) :**

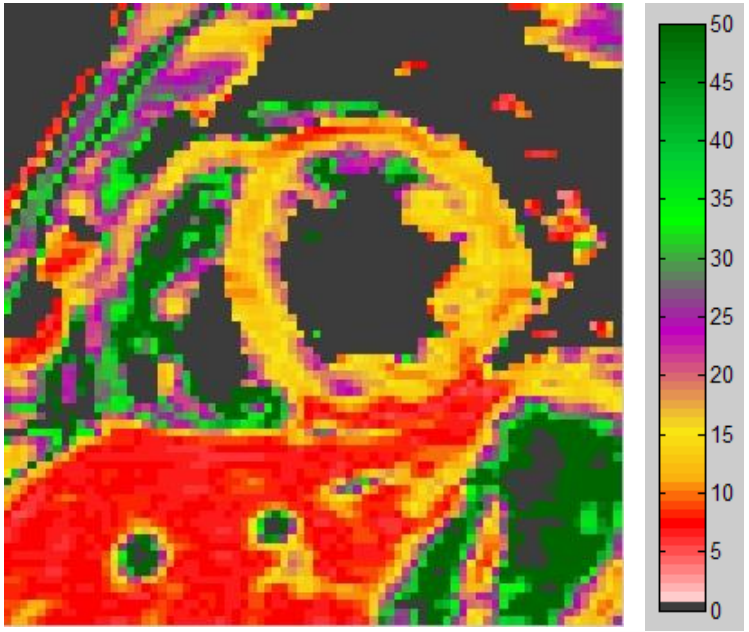
  - MRI T2* < 20 ms.

  - Increase myocardial dysfunction

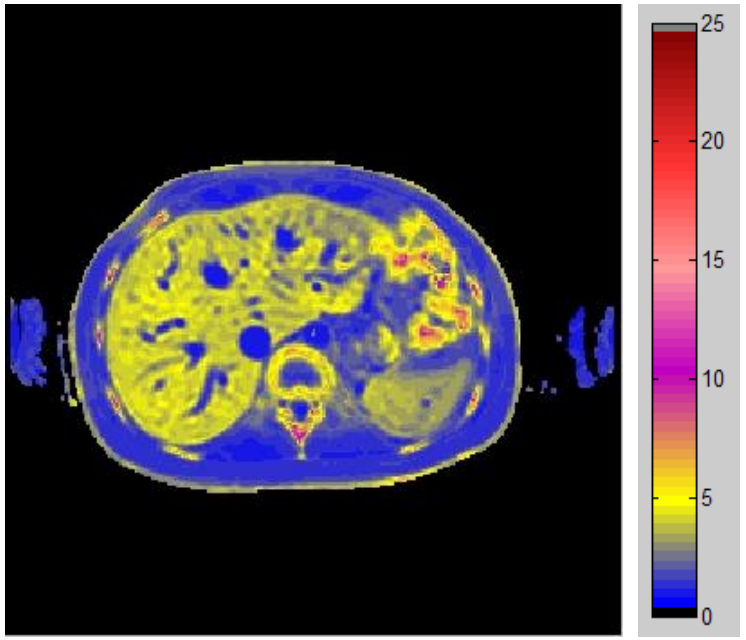
MRI



MRI: T2* & LIC



T2* = 14.8 ms



LIC = 4.5 mg/g dw

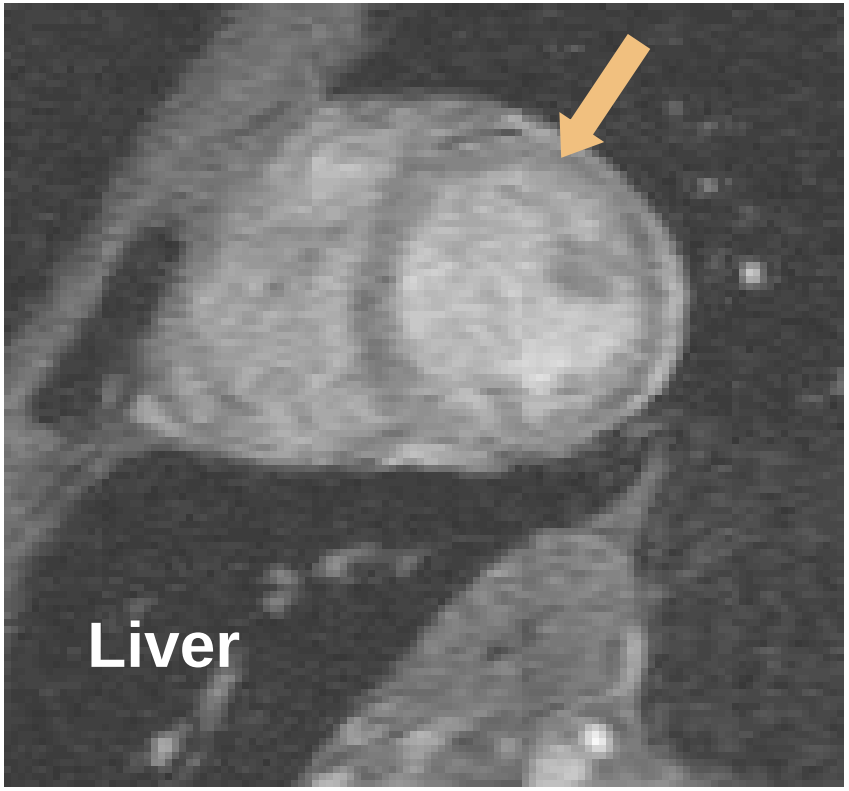
Viprakasit V & Saiviroonporn P. J Comput Assist Tomogr 2011;35:375–381.

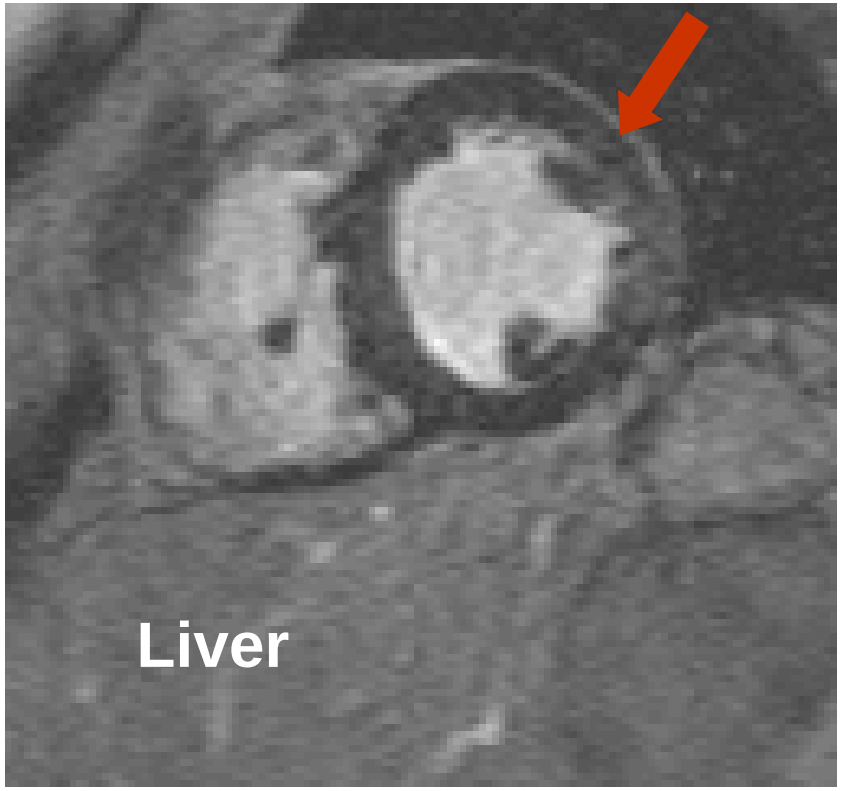
Thresholds for parameters used to evaluate iron overload

Parameter	Normal	Iron-overloaded state		
		Mild	Moderate	Severe
LIC, mg Fe/g dw	<1.8	1.8–7	7-15	>15
Serum ferritin, ng/mL	<300	>1000 to <2500		>2500
Myocardial T2*, ms	>20	20 to 10		<10

Increased risk of complications/cardiac disease

Lack of Correlation: Liver and Cardiac Iron



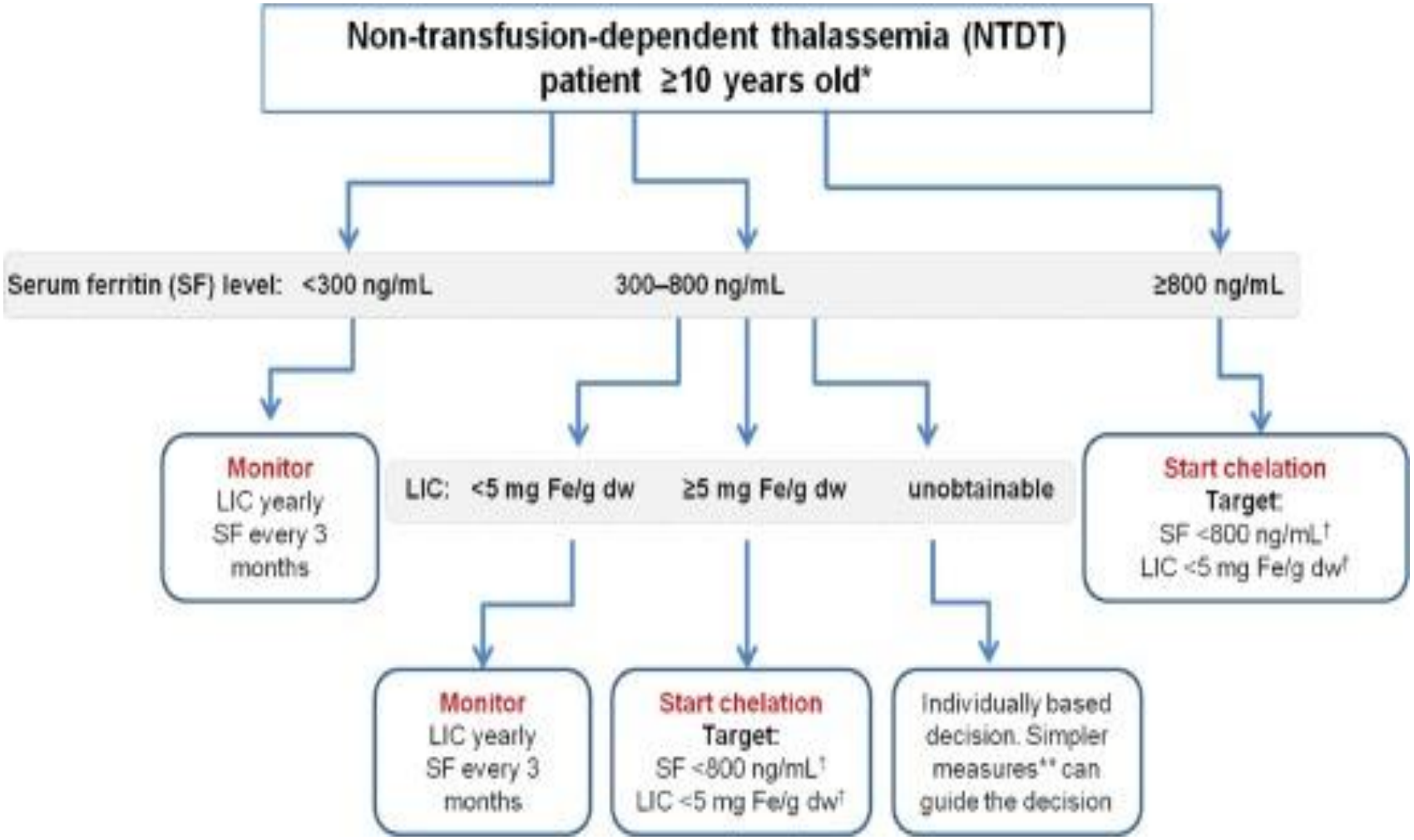


Iron chelation in Thalassemia

Indication on iron chelation in TDT

- Regular trasnfusion >1 yr. (10-20 units of PRC)
- Ferritin > 1,000 ng/ml
- LIC > 7 mg. Fe/ gm.dw
- MRI cardiac T2* > 20 msec.

NTDT


Non-transfusion-dependent thalassemia (NTDT) patient ≥10 years old*
Serum ferritin (SF) level: <300 ng/mL
300–800 ng/mL
≥800 ng/mL
Monitor
LIC yearly
SF every 3 months
LIC: <5 mg Fe/g dw
≥5 mg Fe/g dw
unobtainable
Start chelation
Target:
SF <800 ng/mL†
LIC <5 mg Fe/g dw†
Monitor
LIC yearly
SF every 3 months
Start chelation
Target:
SF <800 ng/mL†
LIC <5 mg Fe/g dw†
Individually based decision. Simpler measures** can guide the decision

Comparison of chelators

Property	DFO	DFP	DFX
Usual dose (mg/kg/day)	20–60	75–100	20–40
Route	s.c., i.v. (8–12 hours, 5 days/week)	Oral 3 times daily	Oral Once daily
Half-life	20–30 minutes	3–4 hours	8–16 hours
Excretion	Urinary, Fecal	Urinary	Fecal
Main adverse effects in PI	Local reactions, ophthalmological, auditory, growth retardation, allergic	Gastrointestinal disturbances, agranulocytosis/ neutropenia, arthralgia, elevated liver enzymes	Gastrointestinal disturbances, rash, mild non-progressive creatinine increase, elevated liver enzymes, ophthalmological, auditory
Age (yrs)	$\geq$ 3	$\geq$ 6	$\geq$ 2

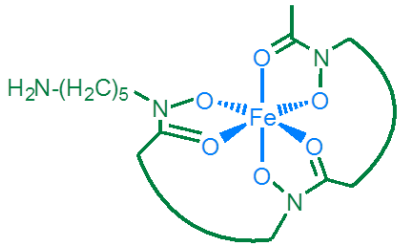
Deferoxamine

- Reference treatment for transfusional iron overload
- Reduces morbidity and mortality
- Specific affinity for Fe3+
- High chelating efficiency
- Requires the use of subcutaneous needles and infusion pumps
- SC or IV administered

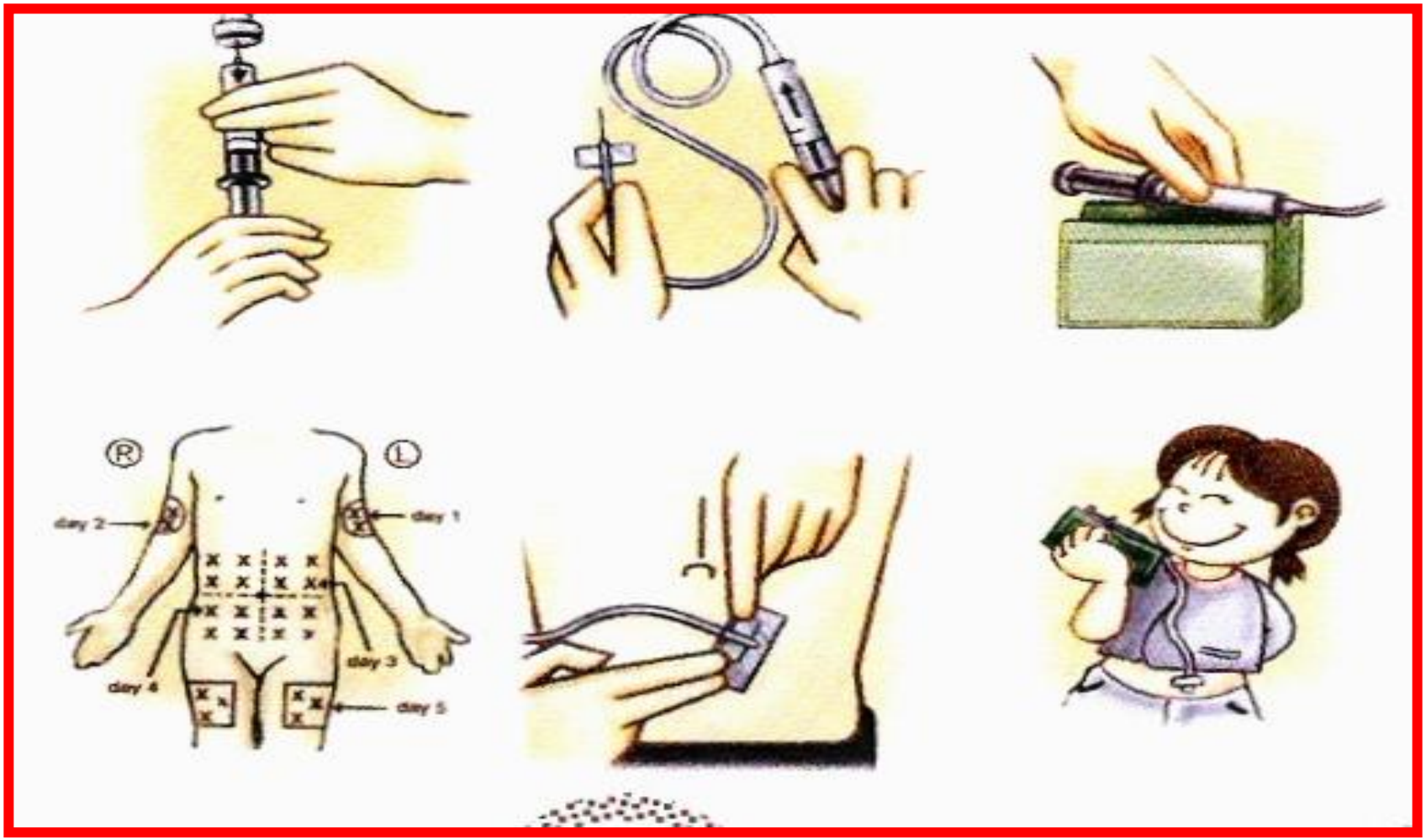
  (8–12 hours, 5 days/week)

DFO

Hexadentate (1:1); high MW

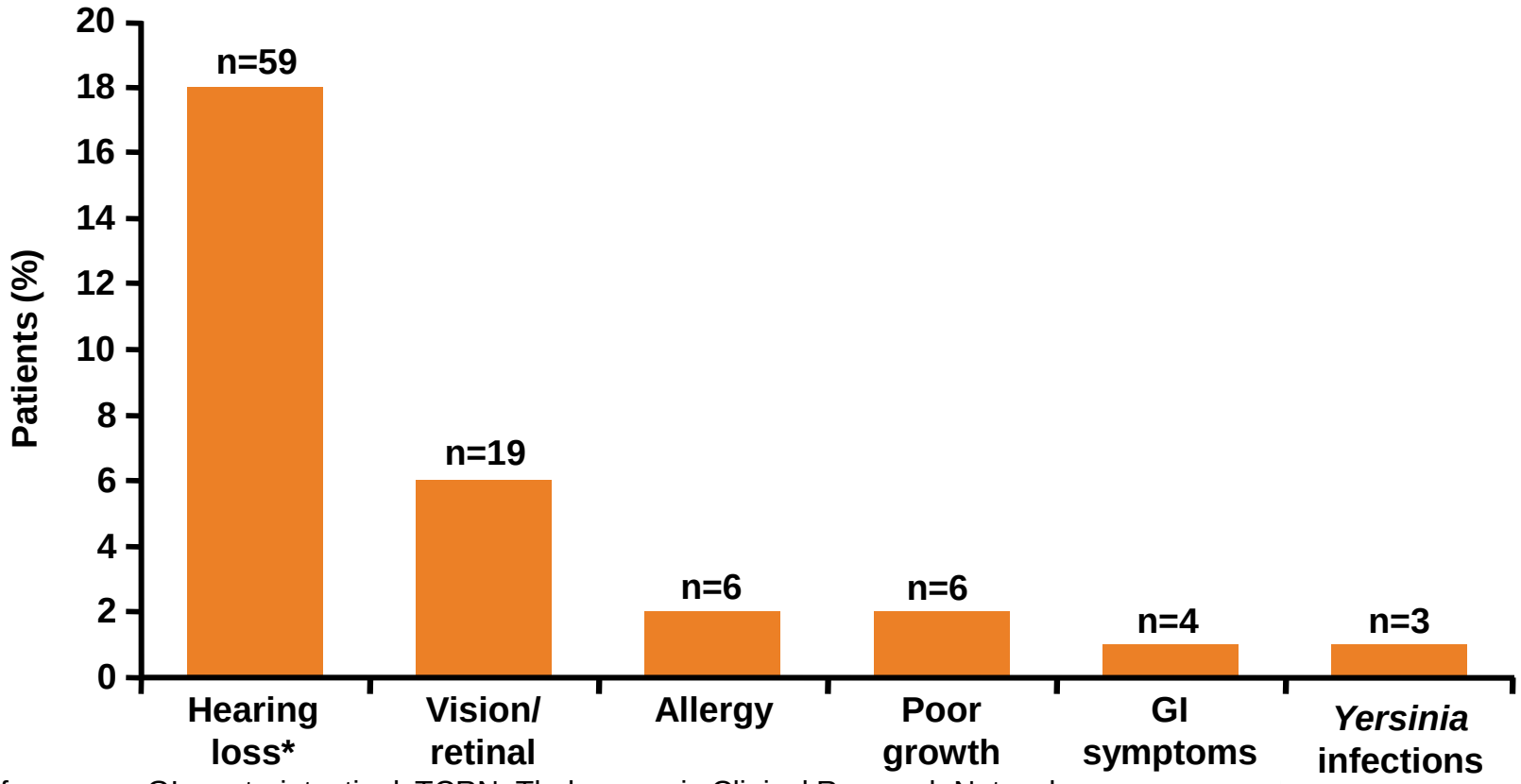


Desferrioxamine.



Common AEs with DFO therapy

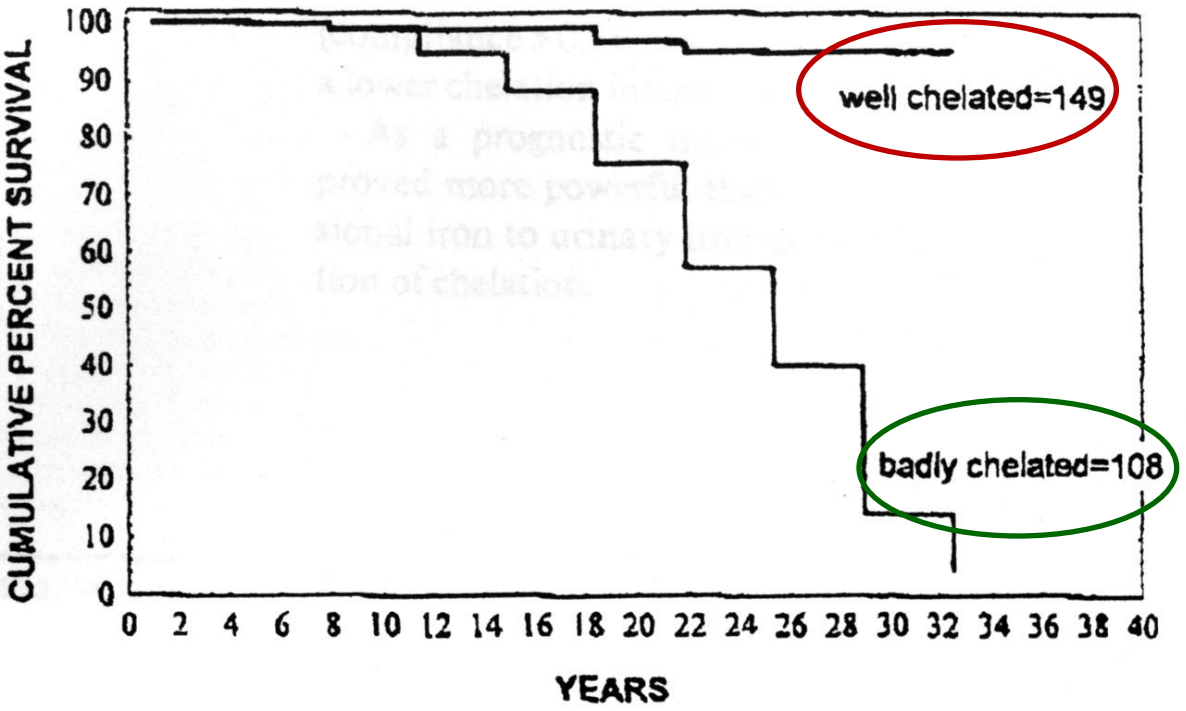
- Cross-sectional study of 328 patients with β-thalassemia major in the National Institute of Health-sponsored TCRN registry who had received DFO therapy



*High frequency. GI, gastrointestinal; TCRN, Thalassaemia Clinical Research Network

Cunningham MJ *et al*. *Blood* 2004;104:34–39

Survival in Patients with Thalassemia Treated with Deferoxamine

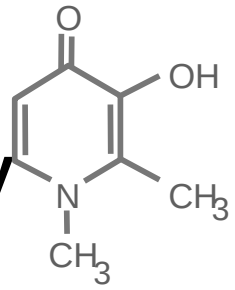


Kaplan-Meier analysis of the survival of 257 consecutive patients with transfusion-dependent thalassemia, according to chelation patterns.
Well chelated. DFO infusions>250/year; n=149; age 17.8±6.5 years; deaths 3 (2%)
Poorly chelated.DFO infusions<250/year; n=108; age 19.7±5.9 years; deaths,58 (54%).

Gabutti and Piga, Acta Hematol, 1996

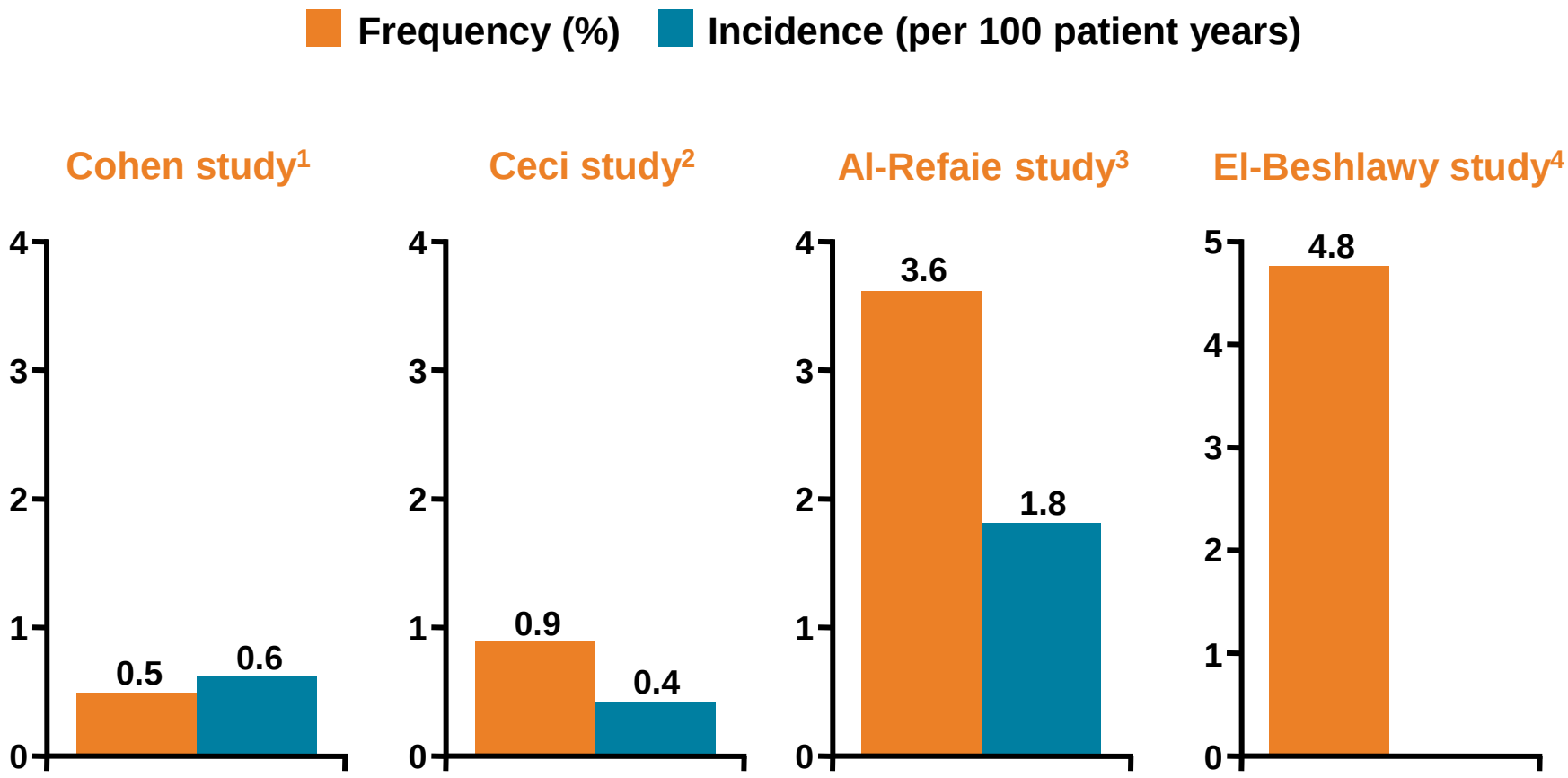
Deferiprone

- **Dosage and administration**
  - **Total daily dose 75-100 mg/kg body weight**
  - **Administered orally**
  - **3 times per day**



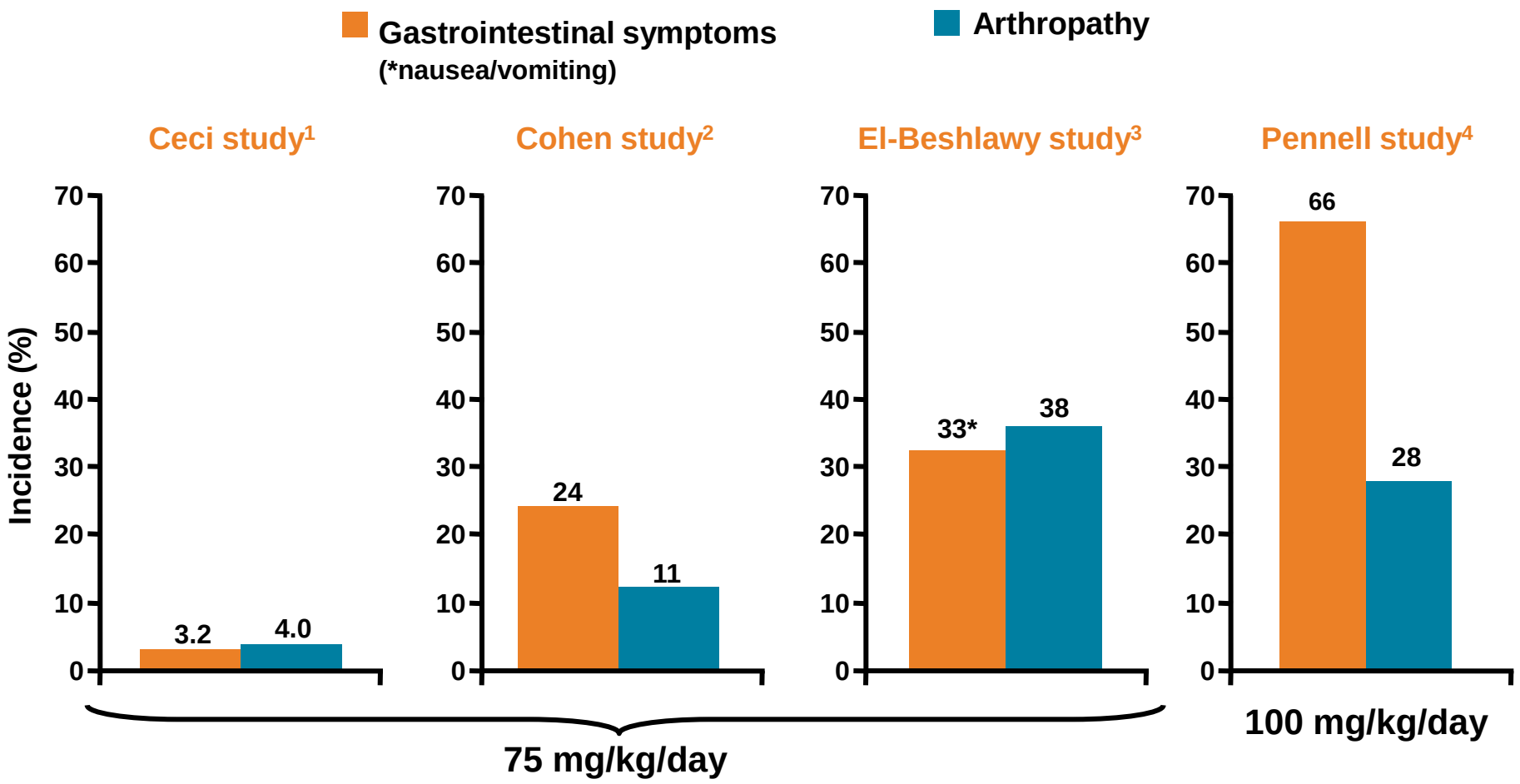
Deferiprone
Bidentate (3:1); low MW

Agranulocytosis with Deferiprone therapy



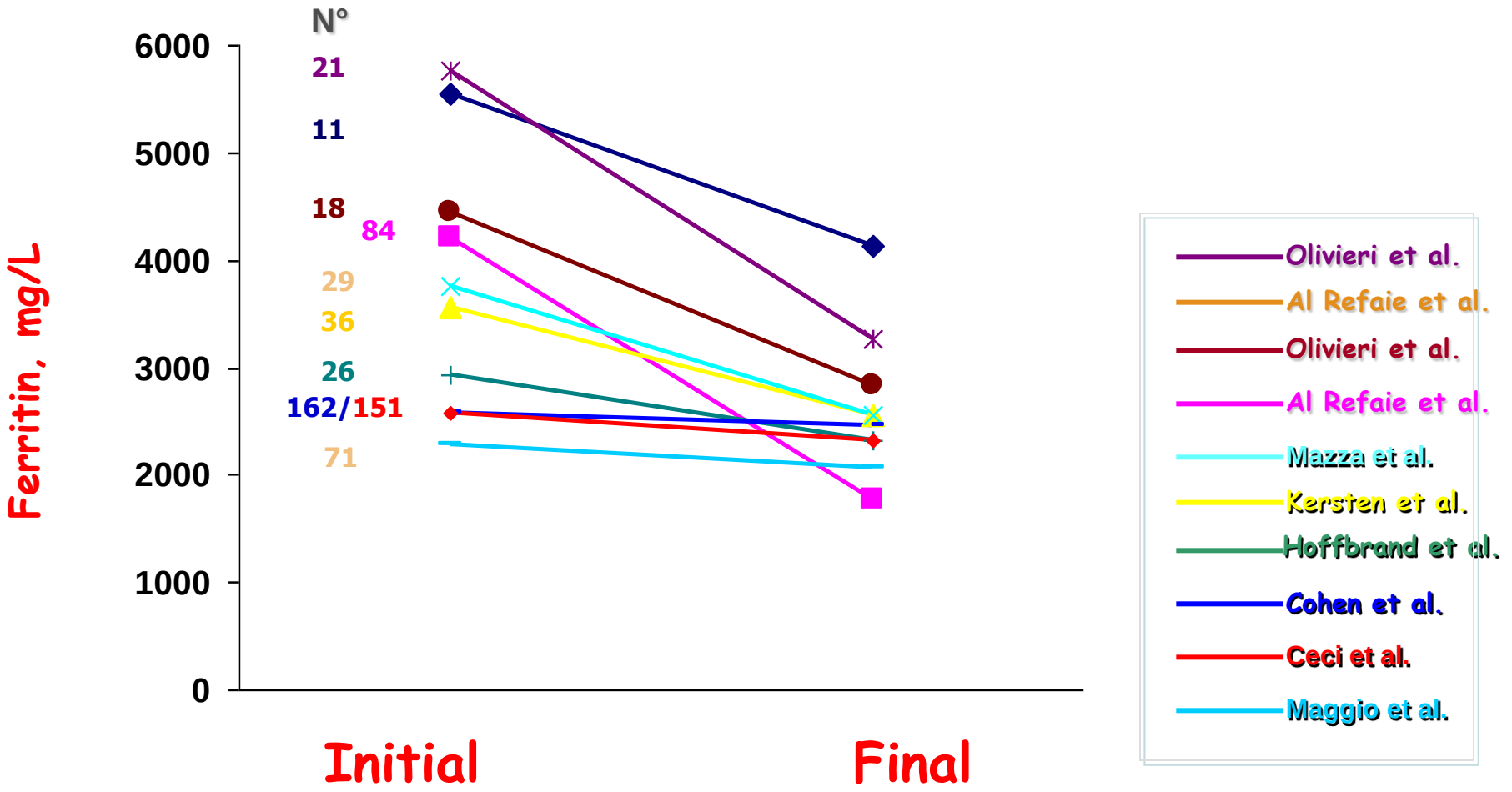
[1]Cohen AR *et al*. *Br J Haematol* 2000;108:305–312; [2]Ceci A *et al*. *Br J Haematol* 2002;118:330–336;
[3]Al-Refaie FN *et al*. *Br J Haematol* 1995;91:224–229; [4]El-Beshlawy A *et al*. *Ann Hematol* 2008;87:545–550

Common side effects with Deferiprone therapy



[1]Ceci A *et al*. *Br J Haematol* 2002;118:330–336; [2]Cohen AR *et al*. *Br J Haematol* 2000;108:305–312;
[3]El-Beshlawy A *et al*. *Ann Hematol* 2008;87:545–550; [4]Pennell DJ *et al*. *Blood* 2006;107:3738–3741

Effect of Deferiprone on Serum Ferritin Levels



Hoffbrand AV. et al, Blood-2003

Deferasirox

- Iron chelator
  - An oral, dispersible tablet
  - Administered once daily
  - Highly specific for iron[1]
- Chelated iron excreted mainly in feces

  (<10% in urine)

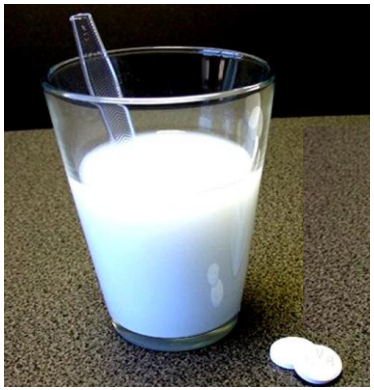
Deferasirox is an oral chelator that provides 24-hour total body chelation coverage with once-daily dosing

***Each deferasirox molecule occupies three coordination sites of a Fe^{3+} atom**

[1]Nick H *et al*. *Curr Med Chem* 2003;10:1065–1076

Method of Administration: Preparation

- Must be taken once daily on an **empty stomach** at least 30 minutes before food, preferably at the **same time each day**
- Stir tablets into **water or apple or orange juice**



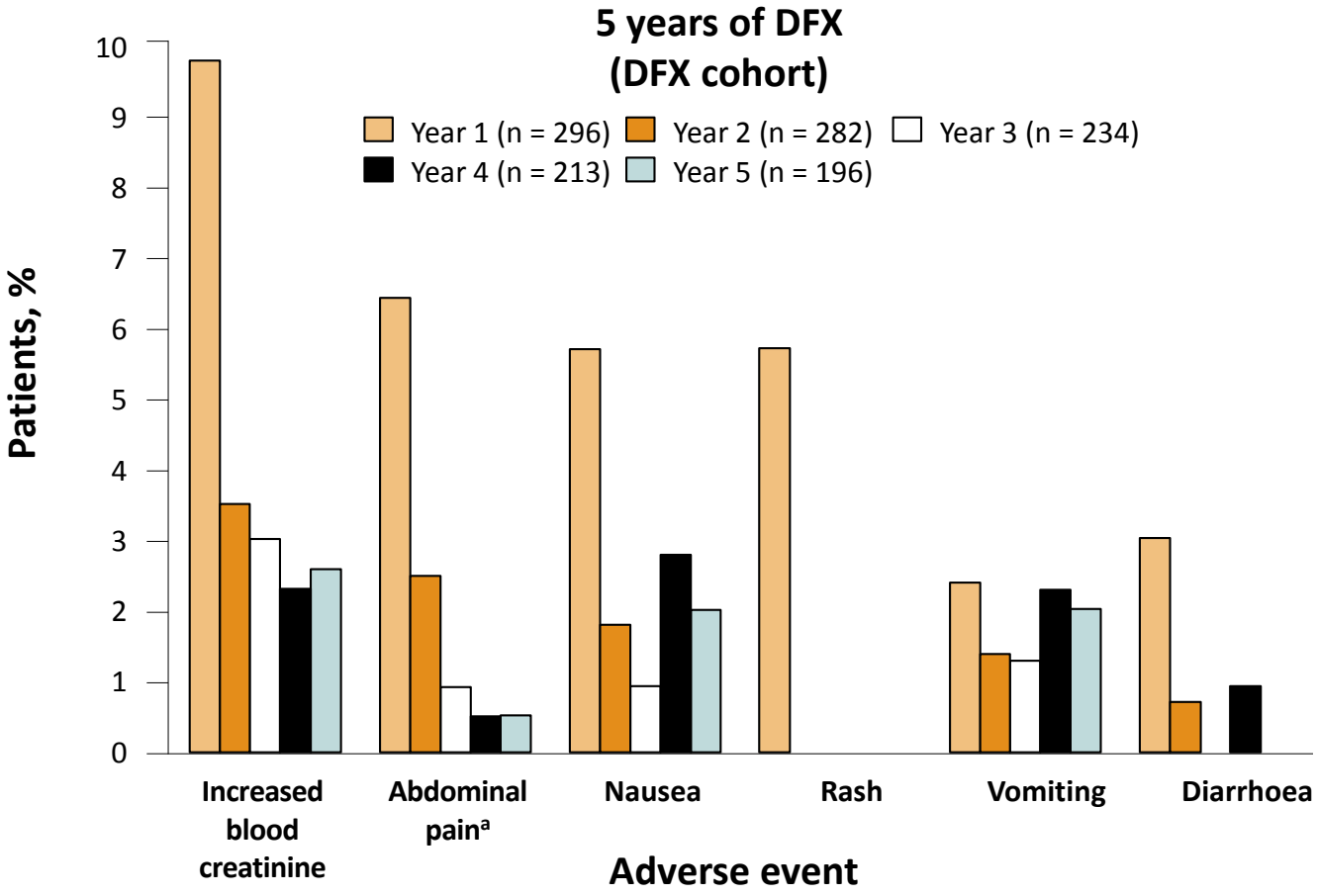
Drop.

Stir 3 minutes.

Drink completely.

Wait 30 minutes before eating.

Deferasirox has been proven safe over 5 years in patients with β-thalassaemia: Study 107

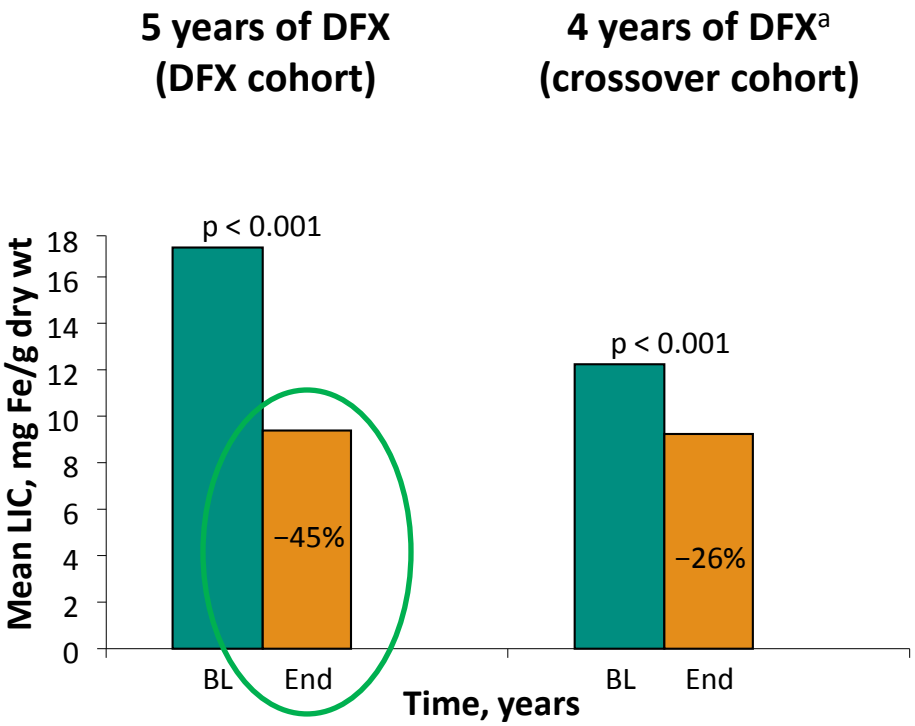


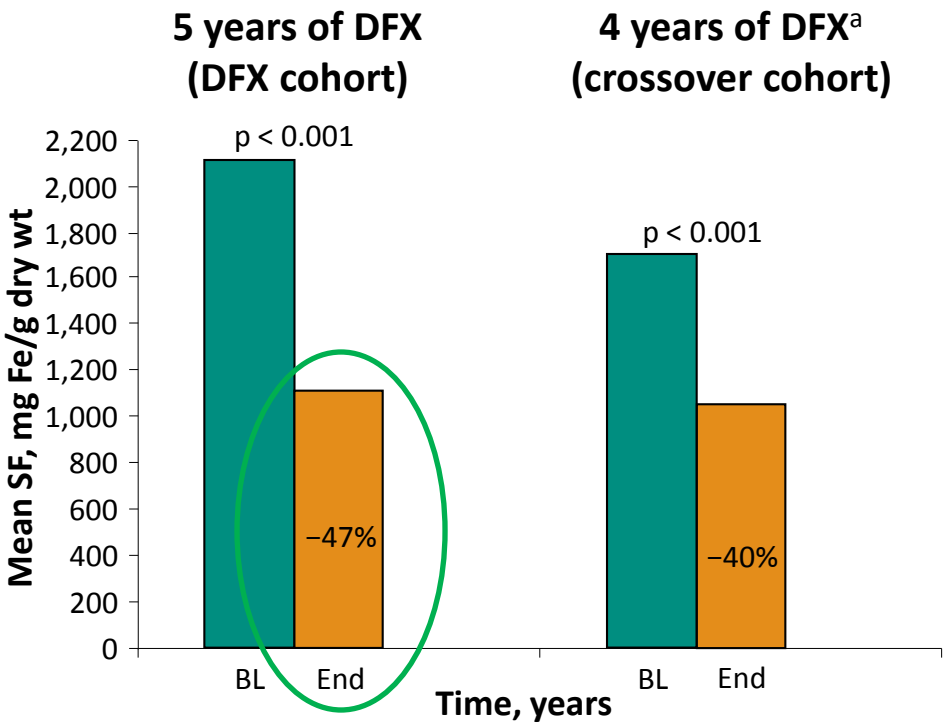
The frequency of investigator-reported AEs decreased over long-term treatment

[a] Reports of abdominal pain and abdominal pain (upper) are combined and presented as abdominal pain.
AE, adverse event.

Cappellini MD, et al. Blood. 2011;118:884-93.

Deferasirox reduced LIC by 45% over 5 years in severely iron-overloaded patients: Study 107



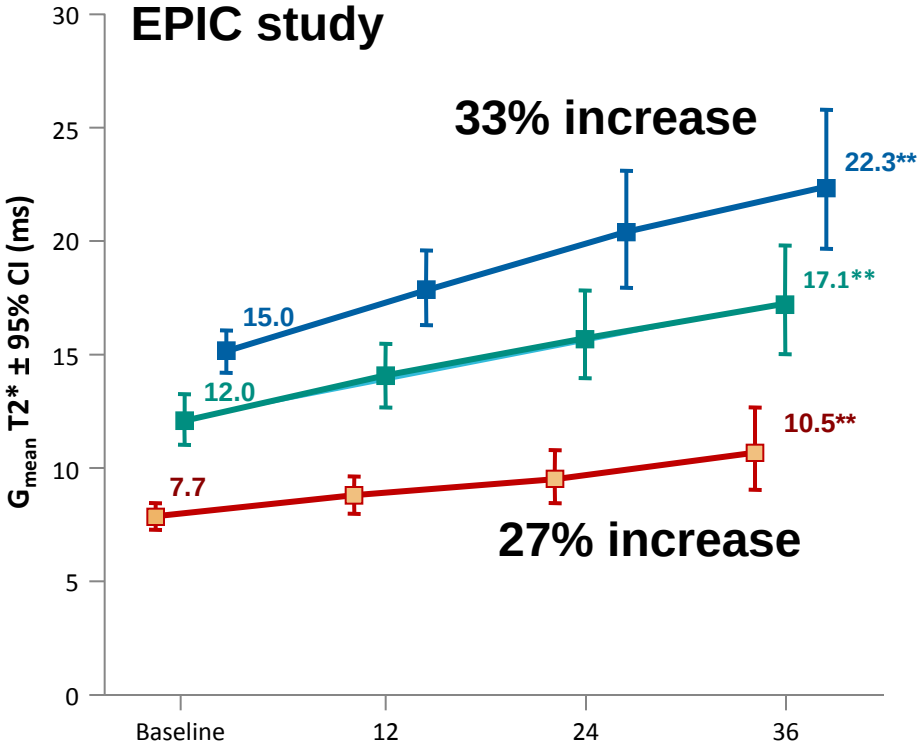


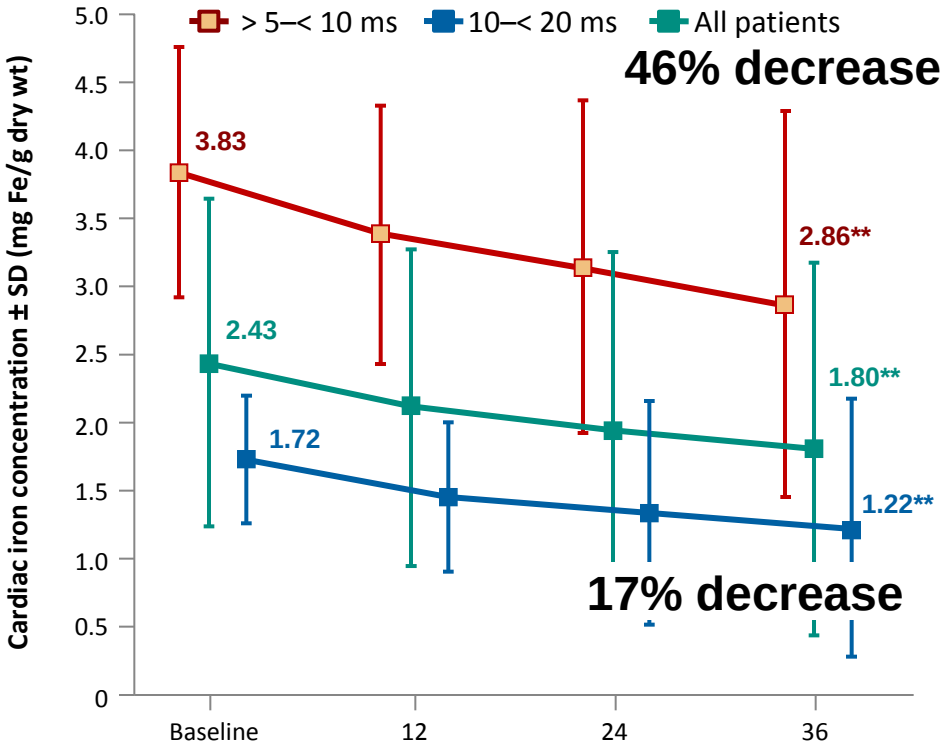
Deferasirox significantly decreased mean LIC by 7.8 ± 11.2 mg Fe/g dry wt (p < 0.001) and 3.1 ± 7.9 mg Fe/g dry wt (p < 0.001) over 5 and 4 years of therapy, respectively

Study 107E: 5 years, phase 3, randomized study in 555 patients with β-thalassaemia and transfusional haemosiderosis.
LIC assessment: biopsy or SQUID. BL: at start of DFX treatment.
[a] Crossover cohort: 1-year DFO (core – not shown); 4-year DFX (extension).
p values = one-sided.

Cappellini MD, et al. Blood. 2011;118:884-93.

Change in myocardial T2* and myocardial iron over 3 years with DFX





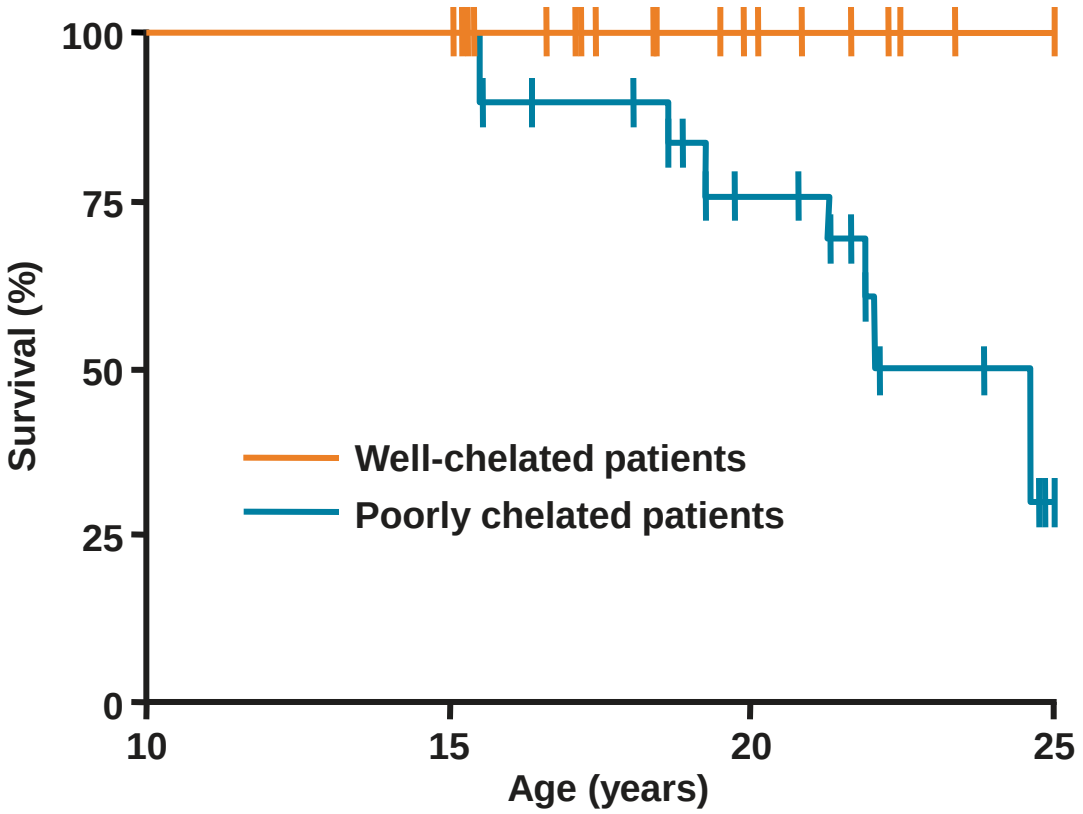
Patients, n								
< 10 ms	24	24	24	24	24	24	24	24
10–< 20 ms	47	47	47	44	47	47	47	44
All patients	71	71	71	68	71	71	71	68

68% of patients with baseline T2* 10–< 20 ms normalized to T2* ≥ 20 ms

50% of patients with T2* > 5–< 10 ms improved to 10–< 20 ms

**p <0.001 versus baseline.

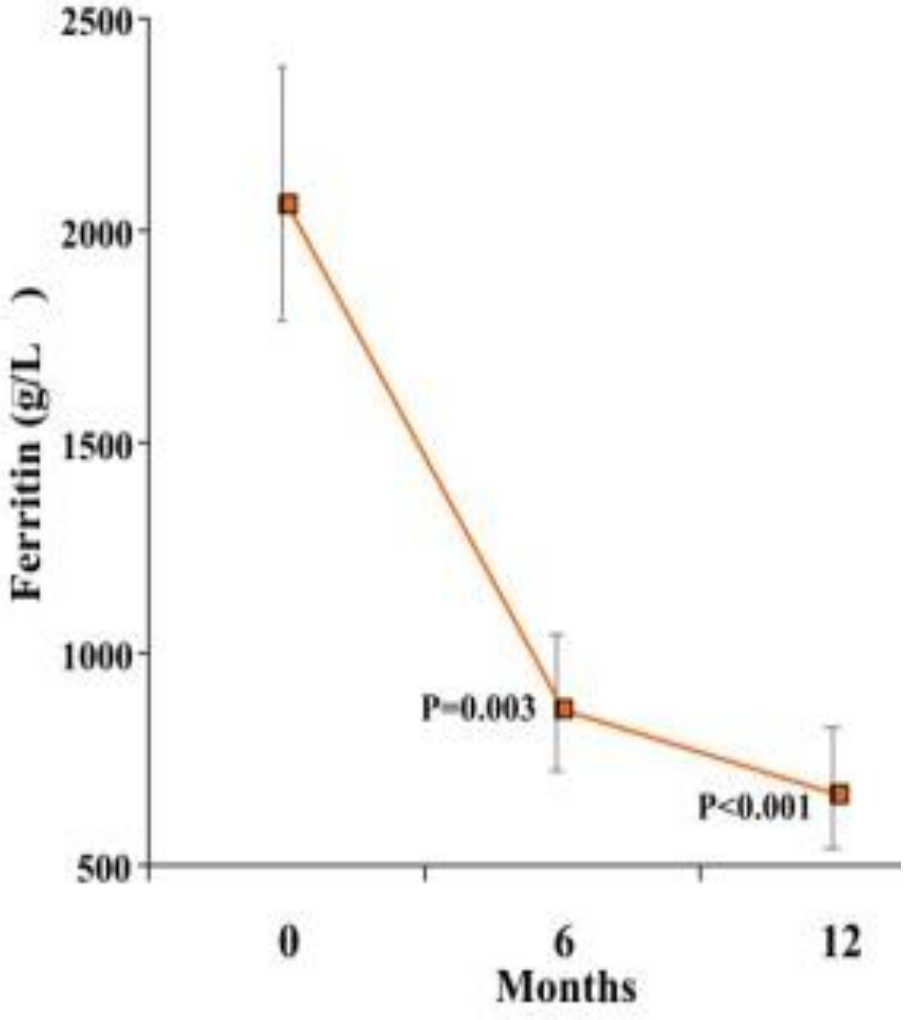
Patient survival correlates with compliance to chelation therapy

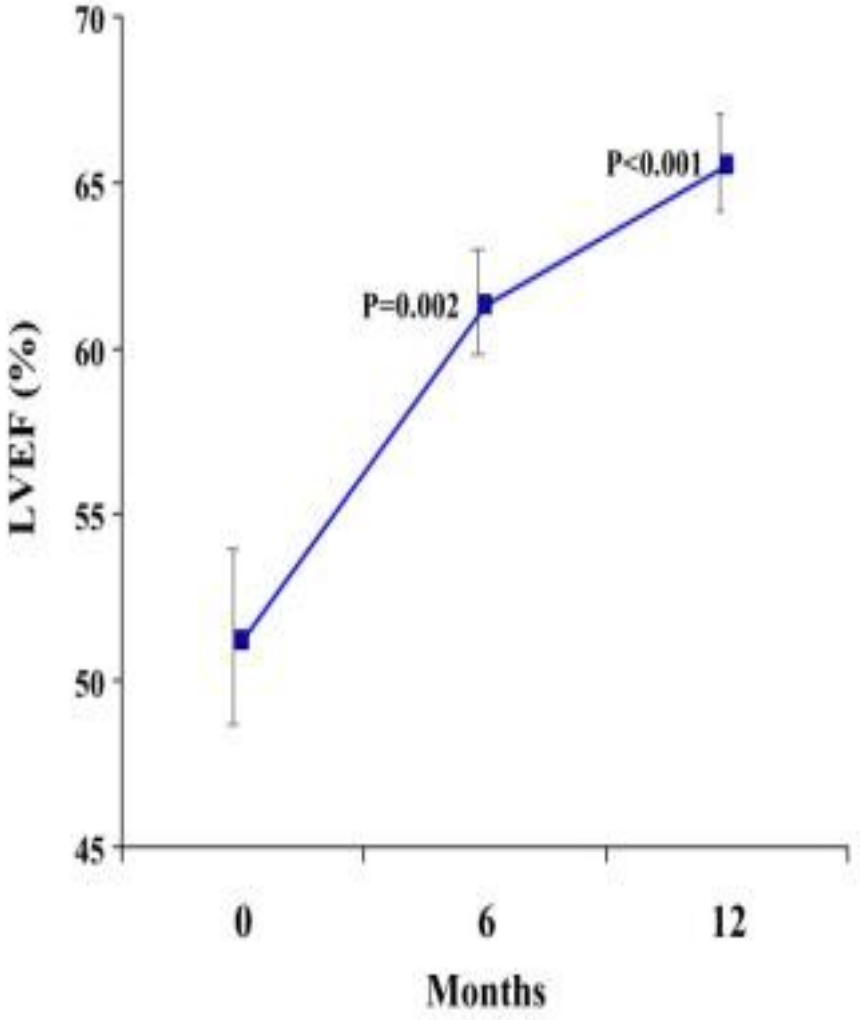


Probability of survival to at least 25 years of age in poorly chelated patients was just one-third that of patients whose iron levels were well managed

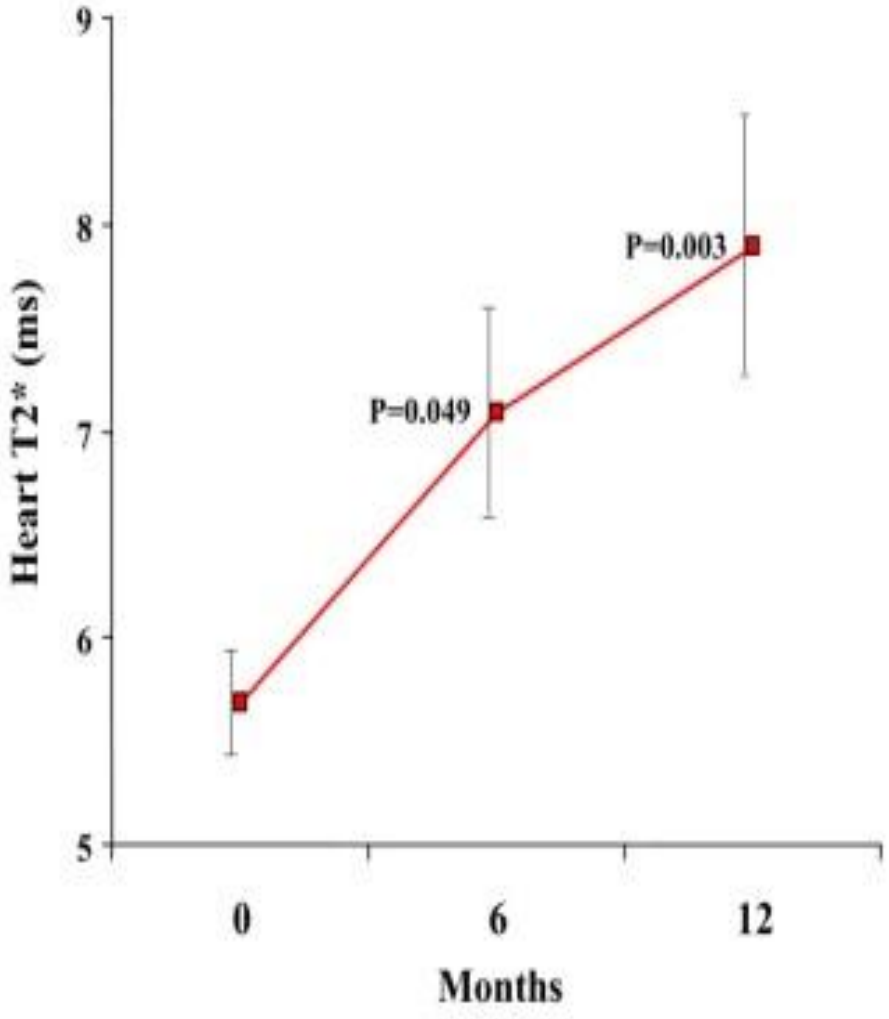
Brittenham GM *et al*. *N Engl J Med* 1994;331:567–573

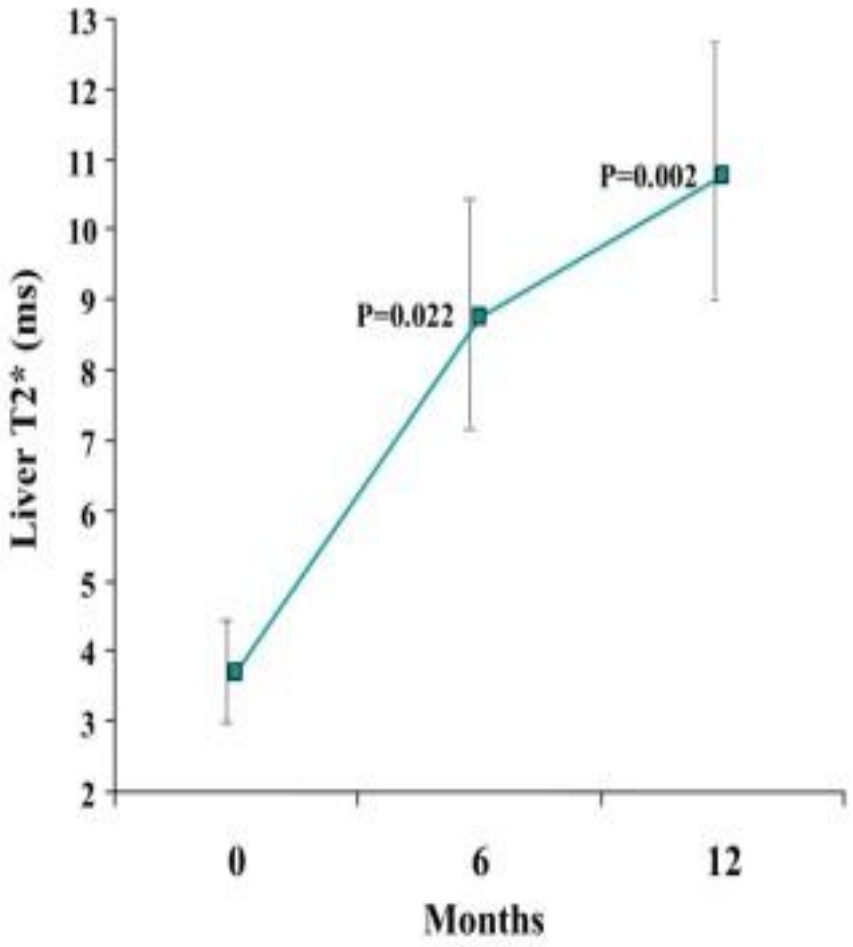
Effects of combined therapy (desferioxamine/deferiprone) in heavily iron laden patients after 12 months of continuous therapy; Note gradual decrease of ferritin levels (left) and clear increase of left ventricular ejection fraction (right)



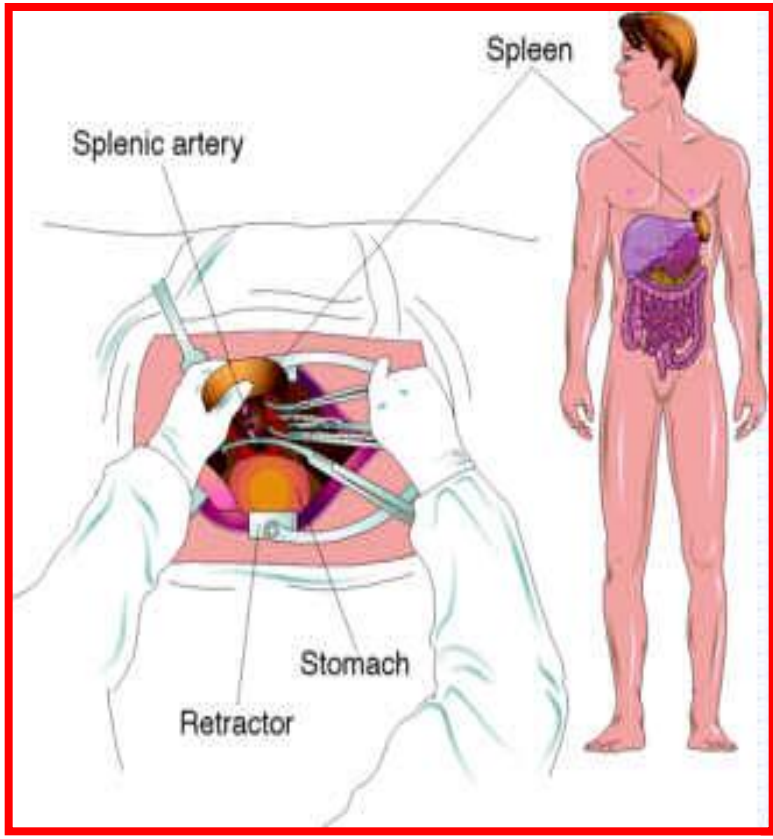


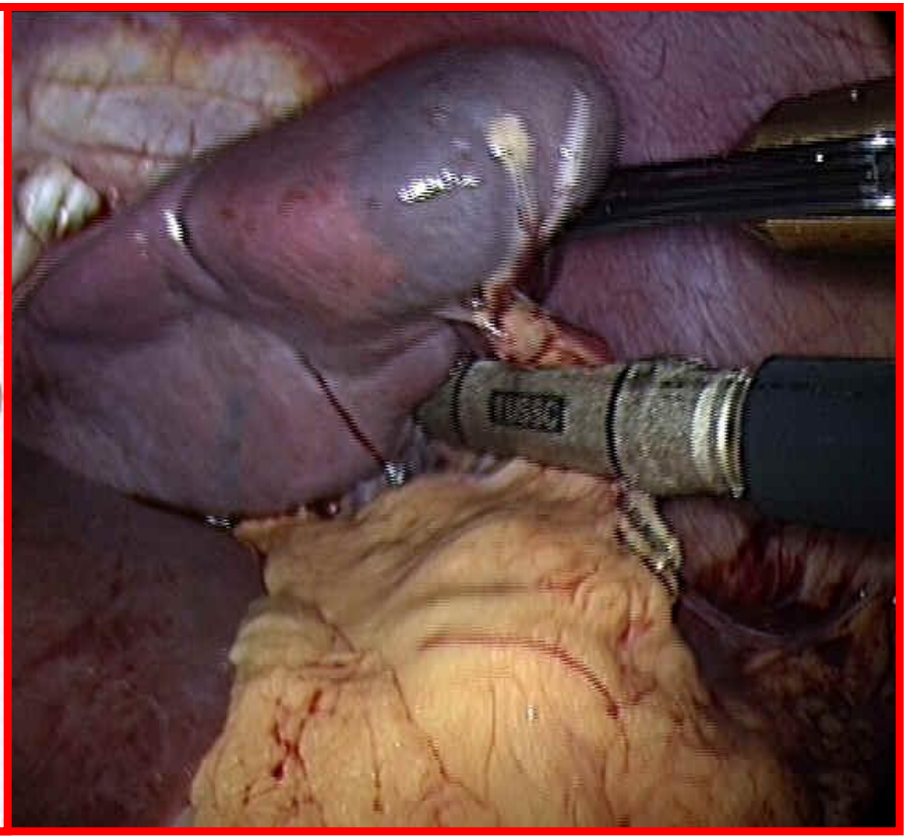
Effects of combined therapy (desferioxamine/deferiprone) in heavily iron laden patients after 12 months of continuous therapy; Note gradual increase of Heart (left) and liver (right) T2* values





Splenectomy





Indication for splenectomy

- Painful or splenomagaly
- Hypersplenic with pancytopenia
- Increasing RBC transfusion
  - > 200 ml / kg / yr
  - ↑ 50 % of usual requirement
- Severe phenotype of Hb H disease

Effect of splenectomy

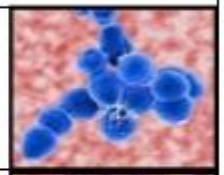
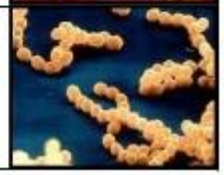
- ↑ Plt count
- ↑ Nucreated red cell
- ↓ Blood requirements(transient)
- ↑ Risk of pulmonary hypertension : Aspirin or anticoagulant
- ↓ Protein C, S

Effect of splenectomy

- ↑ Risk of infection

  - **Risk of sepsis 1-2 %**

  - Polyvalent pneumococcal and conjugateH. inifuezae vaccine 14 days before or after splenectomy

Commonly associated pathogen	
Streptococcus pneumoniae	
Haemophilus influenzae	
Neisseria meningitidis	

Splenectomy

- Avoid child < 5 yrs
- ASA 2-4 mg/kg (plt > 800,000/mm^3)
- Post splenectomy :

  Penicillin (250) 1*2 long life

  or next 5 yrs.

Hb F stimulation

Hydroxyurea

- Benefit of Hydroxyurea is uneven
- Certain mutations predict better response to hydroxyurea
  - *Xmn*I polymorphism
  - Lepore or δβ-thalassemia
- Patients with extramedullary pseudotumors

- Hydroxyurea starting dose of 10 mg/kg/day, not exceeding 20 mg/kg/day
- Response evaluated after 3 and 6 months of therapy
  - Hemoglobin level increase of >1 g/dl at 6 months
  - Discontinue in patients not showing response

Antioxidant

- Decrease toxic from iron

  (strong oxidannt)

- Vitamin C
- Vitamin E
- Curcumin

Treatment complications

Infection

- URI, dirrhea, pneumonia, GNB sepsis
- **Pythium insidiosum** :
  - Arterial occlusion, gangrene, dead
  - Amputation
- **Post DFO** : Yersinia, Pneumocystic carinii, Mucor mycosis

Liver & Gall Bladder

- Hepatomegaly (Extramedullary erythropoisis)
- Liver cirrhosis (Iron, HBV, HCV)
- Gall stone

  - Increase risks :

    cholecystitis,

    cholangitis

  - Elective surgery

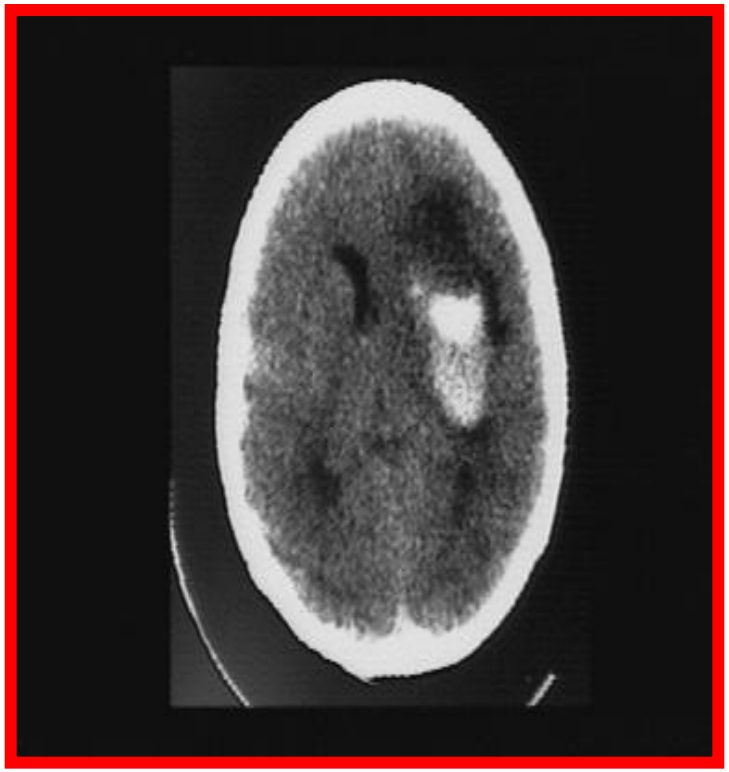
Hypertension

- Post bl transfusion **>,= 2 U.**
- **HCC syndrome**

  (HT, convulsion, hemorrhage)
- Rx. - Only 2 U. - Monitor BP

  - Diuretic

  - Antihypertensive drug



Hypoxemia& pulmonary hypertension

- B thal/ Hb E post splenectomy
- Pulmonary hypertension

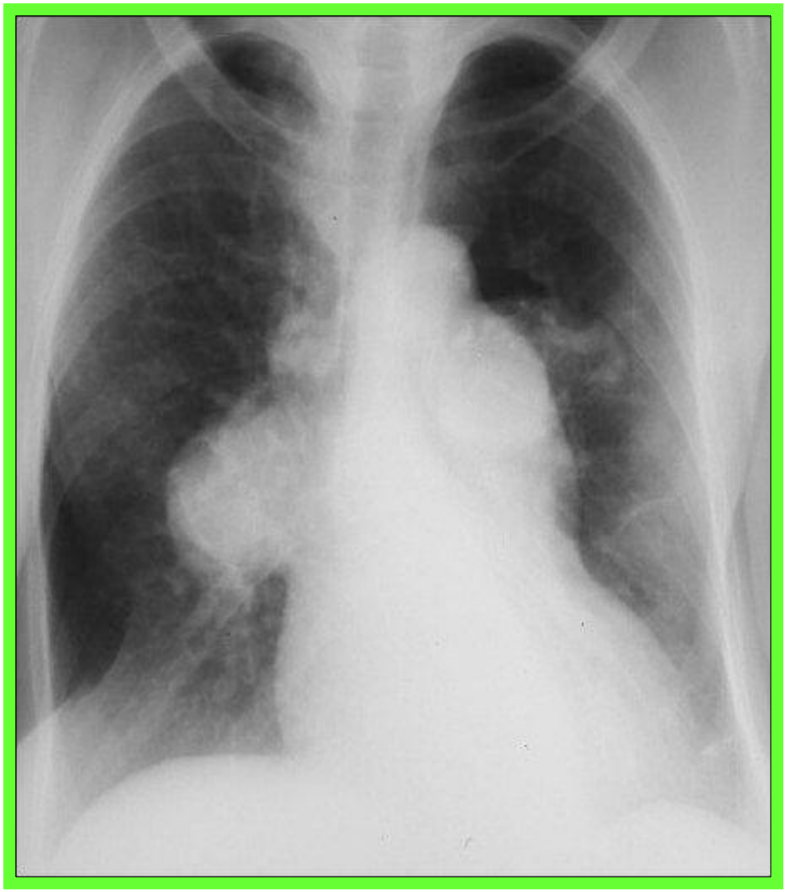
  - thrombocytosis

  - hypercoagulability

    (protein c, s def.)
- Rx. - Low dose ASA

  - Pul. hypertension Rx.

  - Anticoagulant
- .



Extramedullary erythropoiesis

- Anemia increase erythropoiesis

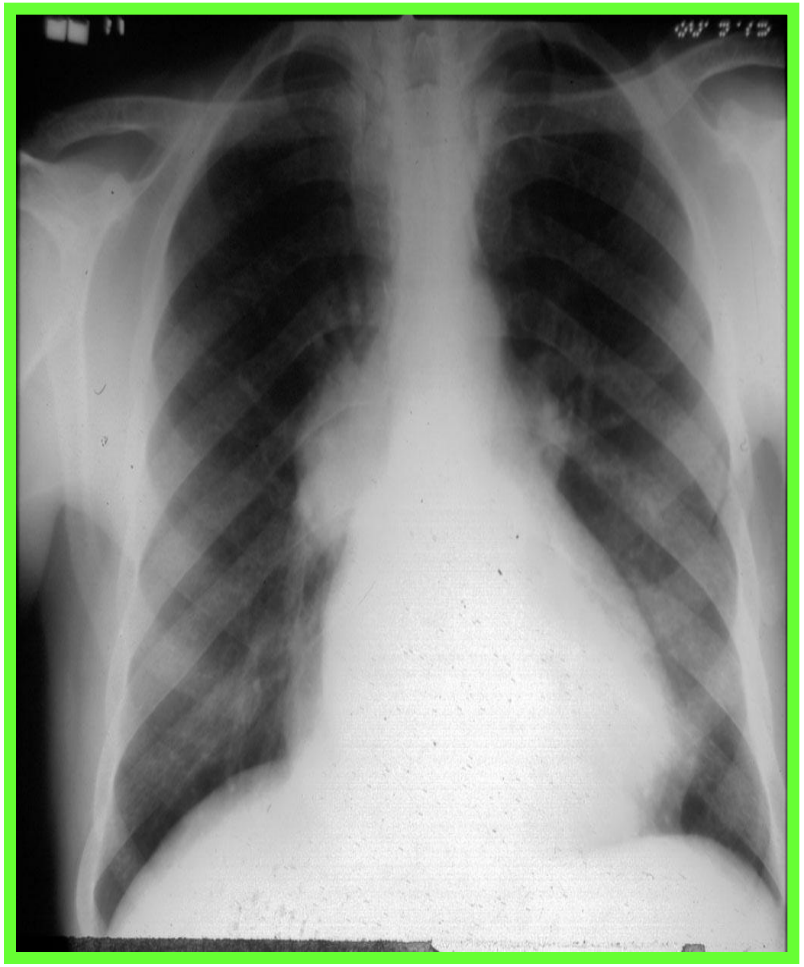
  10-15 times

- Bone resorption
- Fx.(rib, paravetebra)
- Mass : chest , paravetebra, brain
- Rx.

  – Bl. transfusion

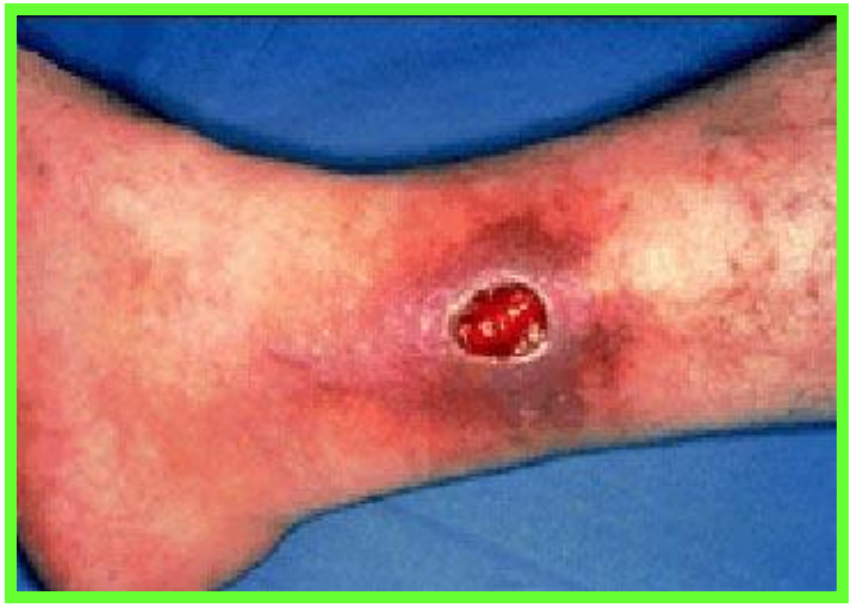
  - RT

  - Hydroxyurea



Chronic leg ulcer

- Commmon :Medial , lateral malleolus
- Poor response : antibiotic, skin graft
- Rx.
  - Blood transfusion
  - Dresssing wound
  - Growth factor : G-CSF



Thank you for your attention.